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Intensive Chemoradiotherapy With Autologous Marrow Transplantation for Small Cell Carcinoma of the Lung[1,2]

P. Stewart,[2,3,*] C. D. Buckner,[3] E. D. Thomas,[2,3] C. Bagley,[3] W. Bensinger,[3] R. A. Clift,[3] F. R. Appelbaum,[3] and J. Sanders[3]

Ten patients with small cell carcinoma of the lung (seven with extensive and three with limited disease) underwent several courses of conventional therapy. The patients were then referred for autologous marrow transplantation, three during a complete response, six during a partial response, and one following no response. The pretransplantation regimen consisted of 120 mg/kg of cyclophosphamide followed by 800–1000 rad of total-body irradiation. In addition, six of the seven patients with extensive disease received high-dose nitrosourea. Following the infusion of cryopreserved autologous marrow, all patients achieved engraftment. Of the three patients without detectable tumor at the time of transplant, two died with tumor present and one survives without recurrence 27 months after transplantation. Of the other seven patients, two had a complete tumor response; both died of interstitial pneumonitis, one without detectable tumor and one with microscopic tumor at autopsy. One of the other five patients had a partial response, but all died of tumor progression. The median survival from initial therapy in patients with extensive disease was 9 months and with limited disease was 18.5 months. [Cancer Treat Rep 67:1055–1059, 1983]

A variety of chemotherapeutic agents and irradiation have been shown to be active in the treatment of small cell carcinoma of the lung (1). Most patients with this disease will have partial response (PR) or complete response (CR), with a small fraction achieving long-term disease-free survival (2,3). However, most patients die of progressive disease within the first 12 months after diagnosis (1). The purpose of this study was to evaluate the toxicity and the antitumor effect of high-dose cyclophosphamide (CY), total-body irradiation (TBI), and autologous marrow transplantation (AMT), following intensive initial chemotherapy.

MATERIALS AND METHODS

Patient Selection

Ten selected patients with small cell carcinoma of the lung treated with several courses of conventional chemotherapy received intensive chemoradiotherapy and AMT. The decision for participation in the autologous transplant study was made by the referring physician and the patient. Elderly and poor-risk patients were less likely to be referred. Initially, the study was restricted to patients with extensive disease, but it was subsequently opened to patients with disease limited to the chest. Eligibility criteria consisted of a Karnofsky performance status > 50, age < 65 years, no involvement of the pelvis with tumor, and no active central nervous system disease.

Protocols and consent forms were approved by the Human Subjects Review Committee of the Fred Hutchinson Cancer Research Center, and informed consent was obtained from patients.

Initial Therapy

Limited disease was defined as localization of disease to one hemithorax, mediastinum, and supraclavicular lymph nodes. All other disease was considered to be extensive. Staging procedures consisted of a chest roent-

[1]Received July 26, 1982; revised June 20, 1983; accepted July 14, 1983.

[2]Supported by Public Health Service grants CA-26828 and CA-18029 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services. E. D. Thomas is the recipient of Research Career Award AI-02425 from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services. P. Stewart is the recipient of a Junior Faculty Clinical Fellowship from the American Cancer Society.

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genogram; cbc; liver function tests; brain, liver, and bone scans; bilateral iliac crest biopsies; and hepatic ultrasound and/or percutaneous liver biopsy for equivocal liver scans. Following staging procedures, patients were given three or four cycles of chemotherapy at approximately 21-day intervals (median, 23 days; range, 20–33). Eight patients (six with extensive and two with limited disease) were treated with three cycles of therapy consisting of the following: CY (1000 mg/m^2) and doxorubicin (50 mg/m^2) on Day 1; and etoposide (200 mg/m^2), vincristine (2 mg), and methotrexate (30 mg/m^2) on Days 1 and 8 (CAVOM). Two patients (Unique Patient Number [UPN] 1217 with extensive and UPN 1317 with limited disease) were treated with four cycles of the following: CY (1000 mg/m^2), doxorubicin (50 mg/m^2), lomustine (50 mg/m^2), and vincristine (2 mg) on Day 1; etoposide (200 mg/m^2) on Days 1, 2, 3, and 4; and methotrexate (30 mg/m^2) on Days 1 and 8 (CACVOM). No dose modifications were made for hematologic toxicity, but cycles could be postponed until counts were normalized. Patient 1167 with extensive disease, superior vena caval obstruction, and pericardial effusion received 1500 rad to the mediastinum and pericardium just prior to initial therapy. Patient 1217 had a positive brain scan and received 3000 rad of whole-brain irradiation at the time of diagnosis. After initial therapy, patients were restaged by repeating all examinations which were positive at diagnosis. Bronchoscopy and liver biopsy were performed in three patients. All patients except UPN 1217 and 1372 received 2400–3000 rad of prophylactic whole-brain irradiation. Patient 1317 with limited disease received 5000 rad of fractionated irradiation over 5 weeks to the mediastinum and hila after achieving a CR with chemotherapy. CR was defined as disappearance of all known tumor previously detected by staging studies or, in the case of equivocal studies, a negative biopsy. PR was defined as a reduction of at least 50% in the product of perpendicular diameters of measurable lesions and no new areas of disease. Responses were defined as unevaluable if the patient had no detectable tumor before transplantation or if there was disease detectable by bone scan which could not be biopsied. Patients unevaluable for response were evaluated for recurrence of disease.

Autologous Marrow Transplantation

Twenty-eight patients (ten with extensive and 18 with limited disease) were referred for marrow cryopreservation using techniques reported elsewhere (4). For the ten patients who had transplants, marrow was stored before initiation of therapy (three patients), after one cycle of therapy (three), after two cycles of therapy (one), and after three cycles of therapy (three). The remaining 18 patients refused AMT; three subsequently received transplants in relapse.

Patients underwent AMT a median of 8 weeks (range, 4–12) after the last induction cycle. The treatment regimens are shown in table 1. All patients received 60 mg/kg of CY on each of 2 successive days, followed in 3–5 days by 1000 rad of TBI delivered at a dose rate of 8 R/minute from opposing dual cobalt sources, except for one patient (UPN 1317) who received 800 rad of TBI. Five of the seven patients with extensive disease received lomustine (250–300 mg/m^2) on each of 2 successive days 3 days prior to treatment with CY, and one patient received carmustine (150 mg/m^2) 1 day following treatment with CY. Nine patients were treated in standard reverse isolation rooms. Patient 1372 was treated in laminar air flow isolation (5). Two patients (UPN 1161 and 1127) received prophylactic granulocyte transfusions (6).

RESULTS

Initial Therapy

Table 2 shows patient characteristics and the results of initial therapy. Six patients with extensive disease achieved a PR, and one achieved a histologically confirmed CR. Two patients with limited disease achieved a CR, and one had no response.

Autologous Marrow Transplantation

Antitumor Effect

Table 1 shows the response following AMT. Two patients with extensive disease (UPN 1012 and 1217) who had a PR to initial therapy achieved a CR; both died of interstitial pneumonitis 3 and 4.5 months after the transplant. One patient (UPN 1012) had microscopic residual tumor of lung and liver and the other (UPN 1217) had no detectable tumor at autopsy. One patient (UPN 1161) who received a transplant after a CR to initial therapy died of hepatic failure at 4 months; at autopsy, tumor was present microscopically in lung and hilar nodes. Two patients (UPN 1122 and 1167) were not evaluable for response because of bone disease, and both showed evidence of disease progression within 4–6 months. Patients 975 and 1052, who had achieved a PR with induction therapy, had no response to AMT and died 4 months after the transplant. The median survival from the beginning of induction therapy for these seven patients with extensive disease was 9 months (range, 6–11); from the time of AMT, it was 4 months (range, 3–8).

Of the three patients with limited disease, one (UPN 1307) received an AMT after failing to respond to initial therapy. This patient achieved a PR and received no further therapy. He died 12 months after AMT from progressive disease; at autopsy, the histology of the tumor was entirely adenocarcinoma. Patient 1317 had received 5000 rad of mediastinal irradiation and was therefore given 800 rather than 1000 rad of TBI. She relapsed with

TABLE 1.—Results of autologous marrow transplantation

UPN	Treatment regimen	Response following transplantation*	Posttransplantation survival (days)	Cause of death	Autopsy findings
		Extensive disease			
975	CY + 1000 rad	NR	141	Tumor progression	
1012	Carmustine (500 mg/m^2), CY + 1000 rad	CR	137	Interstitial pneumonitis	Microscopic tumor
1052	Carmustine (600 mg/m^2), CY + 1000 rad	NR	117	Tumor progression	
1122	Lomustine (150 mg/m^2), CY + 1000 rad	NE	248	Tumor progression	
1161	Carmustine (500 mg/m^2), CY + 1000 rad	NE	125	Cholestatic liver failure	Microscopic tumor
1167	Carmustine (500 mg/m^2), CY + 1000 rad	NE	125	Tumor progression	
1217	Carmustine (500 mg/m^2), CY + 1000 rad	CR	82	Interstitial pneumonitis	No tumor
		Limited disease			
1307	CY + 1000 rad	PR	360	Tumor progression	Adenocarcinoma, no small cell
1317	CY + 800 rad	NE	395	Tumor progression	
1372	CY + 1000 rad	NE	814†	Alive without disease	

*NR = no response; NE = not evaluable.
†As of June 1, 1983.

tumor in the liver and brain, but not in the chest, 10.5 months following AMT. Patient 1372 remains in CR 27 months after AMT, with a Karnofsky performance status of 100%.

Engraftment

No patient failed to engraft. The median number of days to 500/mm^3 granulocytes following AMT was 18 (range, 10–32 days). The median number of days to self-sustaining platelet counts of 20,000/mm^3 and 50,000/mm^3 was 20 (range, 10–37) and 29 (range, 16–87), respectively.

Toxicity

All patients experienced nausea, vomiting, and anorexia with CY + TBI. Moderately severe mucositis was seen in six patients; it was associated with herpes simplex infection in two. Two patients developed a transient rash within 1 week of the transplant, which was thought to be related to antibiotics or CY (7). Hepatotoxic effects were seen in two patients. One patient (UPN 1372) developed a tenfold elevation of SGOT 18 days after transplantation, which persisted for several months but subsequently resolved. One patient (UPN 1161) died of cholestatic liver failure. At the time of diagnosis, this patient had massive metastatic disease to the liver, but normal liver function tests. Four weeks following AMT, she developed hepatomegaly, with a total bilirubin of 3.6 mg/100 ml. She was re-admitted to the hospital for weight loss 3 months following transplantation. Liver function tests were unchanged. She received parenteral and enteral nutrition but she continued to lose weight and developed ascites. She died 125 days after AMT. At autopsy, the liver showed marked centrilobular cholestasis without tumor.

Two patients (UPN 1012 and 1217) developed fatal pneumonitis. At autopsy, the lung showed diffuse alveo-

TABLE 2.—Patient characteristics and responses to chemotherapy

UPN	Age (yrs)	Sites of disease at diagnosis	Response following initial therapy	Sites of disease following therapy	Time from initial therapy to transplant (days)
			Extensive disease		
975	58	Chest, liver	PR	Chest, liver	130
1012	58	Chest, liver	PR	Chest, liver	159
1052	53	Chest, liver, nodes	PR	Chest, liver	141
1122	59	Chest, liver, bone	PR	Liver, bone	97
1161	60	Chest, liver	CR	None	100
1167	47	Chest, liver, bone	PR	Bone	108
1217	61	Chest, nodes, brain	PR	Chest, nodes	138
			Limited disease		
1307	59	Chest	NR*	Chest	92
1317	45	Chest	CR	None	169
1372	43	Chest	CR	None	79

*NR = no response.

lar damage with hyaline membrane formation and interstitial fibrosis. Patient 1217 also had bronchopneumonitis. No other patient had clinical symptoms of respiratory insufficiency or pneumonitis, but all four patients who subsequently came to autopsy having died from tumor (UPN 1122, 1167, and 1307) or hepatic failure (UPN 1161) showed pulmonary congestion, with Patient 1122 also showing diffuse pulmonary fibrosis. There was no histologic or cultural evidence for a viral etiology.

All but one of the patients required iv antibiotics for a median of 19 days (range, 5–27) for fever during the period of neutropenia following transplantation. Two patients had proven infections. The first patient (UPN 1012) developed pseudomonas septicemia and vulvar cellulitis beginning on Day 4, which was treated with antibiotics and granulocyte transfusions. She was discharged from hospital 3 weeks later. The second patient (UPN 1167) developed a perirectal and vulval candida cellulitis on Day 5, which was resolved using amphotericin B.

DISCUSSION

We are encouraged by the evidence of antitumor effect and the ease of engraftment in this small series. The data confirm previous observations that cryopreserved autologous marrow can rescue patients who have received 120 mg/kg of CY and 1000 rad of TBI (8–12). This regimen had a significant antitumor effect in patients with small cell carcinoma of the lung, with two of four evaluable patients with extensive disease achieving a CR after a PR had been obtained by initial chemotherapy. One of these patients had no evidence of tumor at autopsy. Unfortunately, the addition of a nitrosourea to the pretransplant regimen of CY and TBI probably increased the toxicity. Three of six patients died of transplant complications, two with interstitial pneumonitis and one with hepatic failure. The four patients who did not receive a nitrosourea had no serious complications and had a median survival of 1 year. The numbers are too small to permit a comparison of this incidence of interstitial pneumonitis with that seen following syngeneic or allogeneic transplantation (13,14). It is also unknown whether the addition of a nitrosourea contributed significantly to an antitumor effect, but the addition of other chemotherapeutic agents to the CY and TBI regimen has only increased the morbidity and mortality of the procedure in patients with refractory leukemia, without improving the antitumor effect (15). Our experience suggests that the combination of CY, TBI, and nitrosourea should be avoided, especially if significant pulmonary disease and/or tumor is present.

Marrow transplantation facilitates the delivery of otherwise unacceptable doses of CY, TBI, and other therapy. These very high-dose regimens are least likely to be effective in a setting where there is extensive tumor that is resistant to more conventional therapy (16,17). Preliminary studies of high-dose chemotherapy with AMT as initial treatment in small cell cancer have produced a high CR rate, but follow-up is short (18). Another potential application is as consolidation for patients who have achieved CR with conventionally delivered chemotherapy (19). This approach, utilizing CY, TBI, and allogeneic marrow in patients already in remission, has led to an increase in the cure rate in acute leukemia (20,21). We believe patients with small cell lung cancer in complete remission after initial chemotherapy should be considered for further studies, particularly if they have limited disease, since one of our three limited-disease patients is a long-term disease-free survivor and one died of progressive adenocarcinoma without evidence of residual small cell tumor.

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Inhibition of Transplanted Carcinomas in Mice by Retinoids But Not by Vitamin C[1,2]

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A squamous cell carcinoma (ASB XIII) and a large cell carcinoma (ASB XIV) induced from mouse lung cells by chrysotile asbestos were established in serial transplant in BALB/c mice. New hosts were treated with retinoids by ip injection at 10 mg/kg 5 days/week. Growth inhibition of ASB XIII was 58%–64% ($P < 0.005$) after treatments with all-*trans* retinoic acid, 52% after trimethylmethoxyphenyl analog, ethyl ester, 26% (not significant) after 13-*cis* retinoic acid. Growth inhibition of ASB XIV was 39% ($P < 0.02$) after injections of all-*trans* retinoic acid, and 33% ($P > 0.05$) after trimethylmethoxyphenyl analog, ethyl ester. After daily oral administration of 10 mg/kg of all-*trans* retinoic acid in feed, there was 61%–81% inhibition ($P < 0.005$) of ASB XIII. Growth of ASB XIII was not significantly inhibited by daily im injections of 200 mg/kg of vitamin C. [Cancer Treat Rep 67:1061–1065, 1983]

Studies of vitamin A and its analogs (retinoids) for inhibition of induction of cancers in epithelial tissues of experimental animals have been reviewed (1). In addition to inhibition of carcinogenesis, certain retinoids have been reported to inhibit growth of papillomas and carcinomas of the skin in mice (2,3) and to inhibit growth and cause regression of a transplantable chondrosarcoma in rats (4). Biologic effects of 18 retinoids have recently been discussed (5).

In our laboratory, supplementary vitamin A palmitate did not inhibit induction of carcinomas from fetal BALB/c mouse lung tissue transplanted to adult hosts together with methylcholanthrene (6). The tissue transplant technique used in those experiments yielded carcinomas from fetal mouse lung tissue transplanted to adult hosts together with harsh chrysotile asbestos (7). Two of these asbestos-induced carcinomas have been established in serial transplant at intramuscular sites in new hosts (8). One of these tumor lines, identified as ASB XIII, is a squamous cell carcinoma. The other, identified as ASB XIV, is a large cell carcinoma. The present paper reports experiments in which mice bearing transplants of these tumors were treated with three retinoids. Also, in view of claims for inhibition of tumor growth by vitamin C (9), growth of ASB XIII tumors was studied in animals given supplementary vitamin C.

MATERIALS AND METHODS

All experiments were carried out with mice bred in this laboratory from our BALB/c colony. Water and Purina Mouse Chow were provided ad libitum. This feed was obtained in pelleted form and was ground for experiments in which retinoids were added.

For transplant, tumors were removed aseptically and tumor tissue was minced with scalpels. Each new host was implanted with pieces of the mince, aggregating about 2 mm^3, by 13-gauge trocar into right posterior thigh muscles through a skin slit wiped with an antiseptic (Betadine). Such transplants of both ASB XIII and ASB XIV tumors grew progressively in essentially all new hosts, leading to death in about 2 months. Metastases were not found in hosts bearing ASB XIII. Metastases were found in nodes and, extensively, in lungs of hosts bearing ASB XIV.

As a routine, treatment groups consisted of eight young adult mice equally divided as to sex. Tumor diameters and body weights were recorded weekly. Tumors at transplant sites tended to be spherical or ovoid. Diam-

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eters were measured in intact animals with calipers in two dimensions perpendicular to each other. The two diameters were averaged to obtain a single number for each tumor. The number from measurements taken on Day 28 after transplant has been used routinely to calculate the volume of each tumor by the formula: $V = 4.189 r^3$. Mean tumor volume in a group was then calculated from the individual tumor volumes.

Percent inhibition in treatment groups was calculated by the formula:

$$\frac{\text{Mean tumor volume of controls} - \text{Mean tumor volume of treated}}{\text{Mean tumor volume of controls}} \times 100.$$

For statistical analyses, r^3 values for tumors in individual control animals were compared with r^3 values for tumors in individual treated animals to calculate *P* values by the two-tailed Student's t test.

Retinoids and placebos used in this work were supplied by Hoffmann-La Roche, Inc, Nutley, NJ. Chemical structures of retinoids employed have been described (4,5). All-*trans* retinoic acid (Ro 1-5488), trimethylmethoxyphenyl analog, ethyl ester (Ro 10-9359), and 13-*cis* retinoic acid (Ro 4-3780) were received as powders under nitrogen at -70°C and were stored in that way. For injection, 1 week's supply of drug was made up in peanut oil, sonicated for 1 minute in ice water, and stored at 4°C. Injections were given ip 5 days/week. Volume of each injection was 0.1 ml/10 g of body weight.

Ro 1-5488 and Ro 4-3780 were also received in gelatin beadlets at 10% composition. These beadlets, as well as placebo beadlets identical in composition but with 10% corn oil in place of retinoids, were received and stored at -70°C. Consumption of ground Chow meal was found to average 4 g/day/mouse. Considering the average body weight to be 20 g, for a retinoid or placebo dose of 10 mg/kg of body weight, 0.5 g of beadlets was mixed into 999.5 g of meal. Batches of meal with admixture of beadlets were prepared at weekly intervals, stored at 4°C, and provided to mice ad libitum in aluminum cups. Cups were filled daily late in the afternoon to provide fresh retinoids for nocturnal feeding.

For tests with vitamin C, Cevalin (ascorbic acid injection, USP, Eli Lilly and Co) was given by im injection into the leg opposite the tumor-bearing leg. Volume of each injection was 0.02 ml/10 g of body weight.

RESULTS

For the first experiment, growths of ASB XIII and XIV tumors in eight vehicle-treated (peanut oil) control mice were compared with growths in groups of eight mice treated with Ro 1-5488 or Ro 10-9359 at a dose of 10 mg/kg 5 days a week (18 ip injections) starting on

TABLE 1.—Effect of retinoids* on ASB XIII tumor

Treatment	Mean body weight (g)		Tumor diameter (mm) at Day 28			Mean tumor volume (mm^3)	% inhibition	*P* value vs oil
	Start	Day 28	Males	Females	Mean ± SD			
				Experiment 1				
Ro 1-5488	20	22	8.25, 10.75, 12.25, 13.5	10.5, 10.75, 12.75, 13.75	11.6 ± 1.9	862.3	64.4	< 0.005
Ro 10-9359	22	25	12, 13, 16, 16.25	6.25, 9, 12.75, 13.75	12.4 ± 3.4	1175.4	51.8	< 0.05
Peanut oil	20	24	15.5, 16.25, 17, 21.5	13.25, 14.5, 16.5, 16.5	16.4 ± 2.4	2436.5		
				Experiment 2				
Ro 1-5488	26	26	11, 11, 12, 13.5	7.5, 11.5, 12.25, 12.5	11.4 ± 1.7	823.7	57.7	< 0.001
Peanut oil	26	28	12, 14, 16, 17	15.25, 15.5, 15.5, 16.5, 16.5	15.4 ± 1.5	1946.7	21.8†	Not significant†
Untreated	26	26	12, 15.5, 15.5, 16.5, 16.5	15.5, 17.5, 18, 18, 20.5	16.6 ± 2.2	2488.4		
				Experiment 3				
Ro 4-3780	27	29	12.5, 13.25, 15, 15.5, 15.5	13, 13.75, 14, 15.75, 17.5	14.6 ± 1.5	1677.1	26.1	Not significant
Peanut oil	26	29	12.75, 14, 16.75, 17, 20.75	13.75, 15, 16, 16.75, 17.75	16 ± 3.3	2268.2		

*10 mg/kg × 18 ip injections from Day 2 to Day 28 after tumor transplant.
†Vs untreated.

TABLE 2.—Effect of retinoids* on ASB XIV tumor

Treatment	Mean body weight (g)		Tumor diameter (mm) at Day 28			Mean tumor volume (mm^3)	% inhibition	P value vs oil
	Start	Day 28	Males	Females	Mean ± SD			
Ro 1-5488	23	22	6.75, 11.25, 14, 14.5	10, 13, 14.5, 15.5	12.4 ± 2.9	1145	39.1	< 0.02
Ro 10-9359	23	22	12.5, 13.5, 14, 14.25	9.5, 10.5, 12.75, 17.25	13 ± 3.3	1261.4	32.9	Not significant
Peanut oil	23	22	12.5, 14.75, 15, 15	15.75, 15.75, 16, 17	15.2 ± 1.3	1880.8		

* 10 mg/kg × 18 ip injections from Day 2 to Day 26 after tumor transplant.

Day 2 after tumor transplant and ending on Day 28. Findings are presented in tables 1 and 2. Significant tumor growth inhibition was found for each of these retinoids versus ASB XIII and for Ro 1-5488 versus ASB XIV.

In Experiment 2, also shown in table 1, a repeat trial of Ro 1-5488 at the same dosage again showed significant inhibition of ASB XIII. Compared to vehicle-treated controls, no significant difference was found in tumor volume of ASB XIII treated with 10 mg/kg of Ro 4-3780 (Experiment 3, table 1).

Tables 3 and 4 show results of Experiments 4 and 5 in which retinoids were administered in the feed of mice bearing ASB XIII. Controls received feed containing placebo beadlets. Again, 10-mg/kg doses of Ro 1-5488 gave significant inhibition when started 1 or 2 days after tumor transplant. Significant inhibition was also found when the start of treatment was delayed until Day 14, at which time tumors averaged about 9 mm in diameter. Treatments started on Day 2 were significantly more effective ($P < 0.001$) than treatments started on Day 14. When the dose of Ro 1-5488 was increased from 10 to 20 mg/kg, there was further apparent inhibition in tumor volume, but the difference was not significant ($P > 0.10$).

As compared to tumor volumes in animals fed placebo starting on Day 2, there was no significant inhibition after treatment with Ro 4-3780 started on Day 2. Treatment with Ro 4-3780 started on Day 14 gave significant inhibition compared to tumors in controls fed placebo at the same time; however, tumor volumes in these placebo controls were significantly larger than those in untreated controls. There was no significant difference ($P > 0.20$) between tumor volumes in animals whose treatments with Ro 4-3780 were started on Day 2 as compared to Day 14.

In Experiments 1 and 2, the animals were killed at 29 days after transplant and their tumors were removed for examination. Aside from size differences, no gross or histologic differences between treated and con-

TABLE 3.—Effect of oral administration of retinoids* on ASB XIII tumor: Experiment 4

Treatment (Days)	Mean body weight (g)		Tumor diameter (mm) at Day 28			Mean tumor volume (mm^3)	% inhibition	P value vs placebo
	Start	Day 28	Males	Females	Mean ± SD			
Ro 1-5488 (1-28)	22	24	6, 7, 8.5, 10	7.75, 8.75, 10.25, 12	8.8 ± 1.9	400.1	79.9	< 0.001
Ro 1-5488 (14-42)	25	25	10, 11, 12.25, 13.5	12, 12.25, 13.75, 14	12.3 ± 1.4	1017.1	60.8	< 0.001
Ro 4-3780 (1-28)	27	29	12.5, 13.25, 13.5, 16.75	13.75, 14.25, 15.25, 17	14.5 ± 1.7	1662.2	16.5	Not significant
Ro 4-3780 (14-42)	28	29	11.75, 12.25, 13.5, 15, 17.25	12.75, 13.5, 13.5, 14	13.7 ± 1.6	1406.0	45.8	< 0.002
Placebo (1-28)	22	24	13.25, 14.75, 16	13.25, 14, 17.75, 18.5	15.5 ± 2.2	1991.7	(-14.5)†	Not significant†
Placebo (14-42)	24	27	17.5, 17.75, 17.75, 18	13.25, 15.5, 17.5, 18	16.9 ± 1.6	2593.1	(-49)†	< 0.02†
Untreated	25	24	15.25, 16, 16.25, 18	12, 12, 12.75, 13.75, 14.5, 16.25	14.7 ± 2	1740.2		

* 10 mg/kg of body weight.
†Vs untreated.

TABLE 4.—Effect of oral administration of retinoids on ASB XIII tumor: Experiment 5

Treatment	Mean body weight (g)		Tumor diameter (mm) at Day 28			Mean tumor volume (mm^3)	% inhibition	*P* value vs placebo
	Start	Day 28	Males	Females	Mean ± SD			
Ro 1-5488 10 mg/kg on Days 2-29	21	28	9.6, 10.5, 12	10, 11, 13	11 ± 1.3	721.8	70.5	< 0.005
Ro 1-5488 20 mg/kg on Days 2-29	24	25	11	7.5, 8.5, 10, 10.5	9.5 ± 1.4	473.8	80.7	< 0.005
Ro 1-5488 20 mg/kg on Days 14-42	26	25	11, 12.5, 12.5, 14.5	10, 10.5, 10.5, 12.5	11.8 ± 1.4	889.3	63.7	< 0.002
Placebo 20 mg/kg on Days 2-29	25	31	12.5, 16, 16, 17	15.5, 17.5, 20.5	16.4 ± 2.4	2450.3	(-19.9)*	Not significant*
Untreated	27	30	14, 15, 16.5, 21	11, 14, 15	15.2 ± 7.7	2043.8		

*Vs untreated.

trol tumors were observed. In Experiments 4 and 5, tumors were measured at 28 days, but hosts were allowed to live out their lifespans, and length of survival was recorded in days after transplant. Lifespan of individual animals in these experiments ranged from 29 to 80 days, with group mean survival varying from 42.6 to 62.8 days. There were no significant differences in survivorship between any of the treated or control groups, except for the groups treated with 10 or 20 mg/kg of Ro 1-5488 started on Day 2 in Experiment 5. The average survival of each of these treated groups was 62.8 days. Compared to mean survivorship of the placebo controls (51.4 days), significance was $P < 0.002$; however, untreated controls in the same experiment lived a mean of 60.1 days, which was not significantly different from either the placebo group or groups treated with Ro 1-5488.

At doses of retinoids used in all above tests, no evidence of toxicity was found from observation of animals or body weight records. No significant differences were found between tumor sizes in males and females.

Trials of vitamin C on growth of ASB XIII were carried out with groups of ten female mice each. In one group, mice were treated with 200 mg/kg of vitamin C by im injection on the day the tumor was transplanted and daily for 28 days thereafter. In another group, mice were treated with 200 mg/kg of vitamin C by daily im injection for 14 days before the tumor was transplanted and for 28 days thereafter. Two control groups were injected im with physiologic saline in the same volume and on the two schedules used for the vitamin C groups. Tumor volume at 28 days showed no significant difference between the groups given vitamin C and those given saline injections (table 5).

TABLE 5.—Trials of vitamin C on ASB XIII tumor in female mice (200 mg/kg im daily)

Treatment	Mean body weight (g)		Tumor diameter (mm)		Mean tumor volume (mm^3)	% inhibition	*P* value vs saline
	Start	Day 28	Day 28	Mean ± SD			
Vitamin C, 14 days prior to transplant and 28 days after	18	21	13, 13, 13.5, 14, 15.5, 16.25, 16.5, 16.75, 18.75, 22.5	16 ± 2.9	2331.6	(-41.1)	> 0.20
Saline, 14 days prior to transplant and 28 days after	20	23	6, 6, 9, 14, 14.5, 15.5, 16, 16, 18, 19	13.4 ± 4.7	1652.6		
Vitamin C, at transplant through 28 days	20	23	11.5, 12, 12, 14.5, 14.5, 15, 16, 16, 19.5	14.6 ± 2.9	1748.7	6.5	> 0.50
Saline, at transplant through 28 days	20	25	7, 13, 14, 14.5, 14.5, 14.5, 15, 16, 18, 20	14.7 ± 3.4	1871.1		

DISCUSSION

Comparison of tumor volumes showed that all-*trans* retinoic acid was, in all tests, more inhibitory than the ester or 13-*cis* retinoic acid. Significant responses were seen when treatments were started within a day or two after transplant and also when start of treatments was delayed until tumors had become well-established. Greater inhibition was obtained by early administration of 10 mg/kg than by a later dose of 20 mg/kg, although the higher dose gave better results when used at the same period. Oral administration of retinoids gave better response than ip injection. The authors cannot explain the enhanced growth of placebo control tumors versus untreated controls.

Treatment of mice with vitamin C by injection showed no effect on the ASB XIII tumor. Oral administration of vitamin C was not tested.

Trials of various carcinostatic agents have shown increased lifespan of mice bearing ASB XIII and cures of mice bearing ASB XIV after treatments with PCNU (8). Growth inhibitions now reported for retinoid treatments of ASB XIII are comparable to inhibitions of that tumor found in unpublished trials with cyclophosphamide given at 25 mg/kg once a week × 9 and greater than doxorubicin at 2 mg/kg once a week × 4, 5-FU at 50 mg/kg once a week × 8, or methotrexate at 0.75 mg/kg once a week × 8. In regimens cited, none of those four agents significantly increased lifespan of mice bearing ASB XIII.

Recent experiments with mice bearing ASB XIII showed prolongation of life and occasional cures after combined treatments with PCNU and orally administered all-*trans* retinoic acid or trimethylmethoxyphenyl analog, ethyl ester (10).

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Effectiveness of "Two-Route Chemotherapy" Using Cisplatin and Its Antidote, Sodium Thiosulfate, on Lifespan of Rats Bearing Metastatic Liver Tumors[1,2]

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The therapeutic efficacy of "two-route chemotherapy" (TRC) using cisplatin (DDP) and its potent antidote, sodium thiosulfate (STS), was studied on rat metastatic liver tumors. Twenty mg/kg of DDP was given to rats via the hepatic artery in combination with systemic STS at a dose of 1054 mg/kg (100-fold molar ratio to 20 mg/kg of DDP) or at two doses of 1054 mg/kg. As controls, 5 or 4 mg/kg of DDP alone was given intra-arterially or iv. Antitumor effects were evaluated by prolongation in lifespan after the tumor cell inoculation. Side effects were assessed by weight loss, BUN, and serum transaminases after the chemotherapy. TRC resulted in the longest lifespan, with a minimum weight loss and without elevation of BUN or serum transaminases. The therapeutic efficacy of TRC was enhanced by temporary ligation of the portal vein for 5 minutes, performed simultaneously with DDP infusion. Our findings clearly indicate the effectiveness of TRC using intra-arterial DDP in a high dose and in combination with iv STS. [Cancer Treat Rep 67:1067–1074, 1983]

One important factor in cancer chemotherapy is to reduce the side effects of anticancer drugs on normal tissues, including bone marrow, intestine, and kidney. Since Klopp et al (1) treated human head and neck cancers with intra-arterial mechlorethamine, similar intra-arterial treatments with anticancer drugs have been widely prescribed for various regionally confined tumors, in the hope of a selective effect. However, the dose of the anticancer drug is limited, because of side effects after the drug enters the systemic circulation. We established "two-route chemotherapy" (TRC), in which the anticancer drug is injected into the tumor-feeding artery or peritoneal cavity of rats, in combination with its antidote given systemically. Using this approach, the anticancer drug can be administered locally into tumor tissues at a high dose and without systemic toxicity. We reported the effectiveness of this chemotherapy for metastatic liver tumors (2–4), urinary bladder tumors (5,6), and intraperitoneally disseminated tumors (7) in rats. Initially, the effectiveness of TRC was demonstrated in the case of metastatic liver tumors in rats using mechlorethamine *N*-oxide and its antidote, cysteine (2,3). These two agents were given locally through the hepatic artery (mechlorethamine *N*-oxide) and systemically through the femoral vein (cysteine), on the basis that liver tumors are mainly nourished by the hepatic artery and normal liver tissues are mainly nourished by the portal vein (8–12). Recently, we reported the effectiveness of TRC on more advanced metastatic liver tumors in rats using cisplatin (DDP) and its potent antidote, sodium thiosulfate (STS); we assessed effectiveness by evaluating the tumor weight (4). In the present experiment, we studied the effects of TRC on lifespan prolongation, nephrotoxicity, and hepatic toxicity in the same metastatic liver tumor system using DDP and STS.

MATERIALS AND METHODS

Animals, Tumors, and Drugs

Female Wistar-King A (WKA) rats were obtained from the Animal Center of Kyushu University and maintained on a conventional diet and water, ad libitum. Rats weighing 130–150 g at 6–7 weeks of age were used in chemotherapy experiments.

The tumor used was a hepatocellular carcinoma (NH-hepatoma), induced in WKA rats with 3′-methyl-4-(di-

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methylamino)-azobenzene and maintained by serial transfer into the hind limb of WKA rats every 10–11 days. The tumor was excised, minced, suspended in Hanks' balanced salt solution, and passed through a metal sieve to obtain a single-cell suspension. After viable cell counts of the suspension with the trypan blue exclusion test, the cell density was adjusted with salt solution to yield 1×10^6 viable cells/ml. To prepare the animals bearing metastatic liver tumors, rats were anesthetized with ether, laparotomized, and injected with 1 ml of the tumor cell suspension into the mesenteric vein.

DDP (Nippon Kayaku Co, Ltd, Tokyo, Japan) was dissolved in 0.9% NaCl solution to give concentrations of 1.0, 0.25, or 0.2 mg/ml. STS (Wako Pure Chemical Industries, Ltd, Osaka, Japan) was also dissolved in 0.9% NaCl solution at a concentration of 105.4 mg/ml. Each solution was prepared immediately before use.

Chemotherapy Experiments

Chemotherapy experiments were done on visible metastatic liver tumors 0.5–1.0 mm in diameter 6 days after tumor cell inoculation. All rats were anesthetized with ether and laparotomized through a midline incision to verify the existence of metastatic liver tumors, and the following procedures were performed according to each treatment design.

Intrahepatic arterial infusion of DDP was performed through a fine tapered polyethylene catheter inserted into the hepatic artery under an operation microscope (Konan Camera, R & I, K-280, Nishinomiya, Japan), as previously described (2–4). DDP solution was infused at a flow rate of 4.1 ml/minute using an infusion pump (Harvard Apparatus, Model 975E, Boston, MA). After DDP infusion, the catheter was removed and the hepatic artery was ligated. Iv administration of DDP was performed by manual injection into the tail vein. STS solution was given via the femoral vein by manual injection, within a period of about 1.5 minutes. DDP and STS solutions were given in a volume of 2 and 1 ml/100 g of body weight, respectively.

Experiment 1.—Twenty mg/kg of intra-arterial DDP and 1054 mg/kg of iv STS (1:100 at the molar ratio) were given simultaneously (TRC). As controls, 5 mg/kg of DDP alone was given intra-arterially or iv. Laparotomy alone was done on the untreated controls. Four separate experiments were done, using groups of three rats for each experiment.

Experiment 2.—In TRC, 20 mg/kg of DDP was infused intra-arterially, and 1054 mg/kg of iv STS was given twice, 0 and 5 minutes after the initiation of DDP infusion. Control rats were given 4 or 5 mg/kg of DDP alone intra-arterially or iv. In both groups given TRC and intra-arterial DDP alone, some of the rats underwent portal vein ligation (PVL) for 5 minutes, starting just before the DDP infusion. Laparotomy alone, as a sham operation, was performed on the untreated controls. Ten separate experiments were done, using groups of three to four rats for each experiment.

Evaluation of Antitumor Effects and Side Effects

Antitumor effects were evaluated by prolongation in lifespan of rats after tumor cell inoculation. Side effects were evaluated by changes in body weight, BUN, and serum transaminases (SGOT and SGPT). Rats were weighed on Days 1, 3, 6, and 10 after the therapy in all experiments. In Experiment 2, all rats and six sampled rats of each treated group were respectively bled from the tail vein for BUN measurement on Day 4 and for transaminase assay on Days 4, 7, and 10 after the therapy. BUN and transaminases were respectively assessed by the urease method (13) and the modified Reitman-Frankel method (14). Comparison of lifespan and BUN between treated groups was made statistically, using the Wilcoxon test. Changes in body weight and transaminases were statistically analyzed, using Student's t test. To assess tumor cell damage from the therapy and tumor growth after the therapy, histologic

TABLE 1.—Effect of DDP with or without STS on lifespan of rats bearing metastatic liver tumors

Group	No. of rats	Treatment* DDP Dose (mg/kg)	DDP Route	STS	% lifespan† Median (range)	*P* value‡
A	12	20	HA	+	130.5 (108.3–168.2)	-
B	12	5	HA	-	121.1 (98.2–137.5)	< 0.05
C	10	5	TV	-	112.5 (94.7–129.2)	< 0.005

*Treatments were given 6 days after the inoculation of 1×10^6 tumor cells. DDP was given through the hepatic artery (HA), or the tail vein (TV). 1054 mg/kg of STS was injected into the femoral vein concurrently with DDP infusion (+).

†% lifespan after the tumor cell inoculation was calculated according to the equation: % lifespan = $100 \times t/c$, where t is the survival time of the treated rats and c is the survival time of the untreated controls in days. Mean survival of the untreated controls was 23.7 ± 1.4 days after the tumor cell inoculation.

‡Probability compared with Group A was calculated by Wilcoxon test.

TABLE 2.—Effect of DDP with or without STS and temporary PVL on lifespan and BUN level of rats bearing metastatic liver tumors

Group	No. of rats	Treatment* DDP Dose (mg/kg)	Route	STS	PVL	% lifespan†	*P* value compared with group A	*P* value compared with group A2	BUN (mg/100 ml)‡ Median (range)
A1	12	20	HA	+	+	140.2 (104.8–187.5)	–	–	19.3 (14.3–26.4)
A2	14	20	HA	+	–	124.7 (107.0–147.9)	< 0.1	–	19.7 (14.9–75.7)
B1	8§	5	HA	–	+	139.4 (122.5–182.6)	NS	< 0.05	88.2 (52.3–118.4)¶
B2	10	5	HA	–	–	125.6 (113.0–158.3)	< 0.1	NS	32.0 (18.3–107.5)¶
B3	9	4	HA	–	+	121.9 (95.2–139.5)	< 0.05	NS	95.4 (39.7–126.7)¶
B4	10	4	HA	–	–	111.1 (90.5–136.8)	< 0.01	< 0.1	18.4 (13.4–58.6)
C1	12	5	TV	–	–	109.3 (94.3–131.0)	< 0.01	< 0.01	30.9 (11.2–48.2)¶
C2	14	4	TV	–	–	105.5 (88.4–148.8)	< 0.01	< 0.05	25.8 (16.5–48.1)¶

*Treatments were given 6 days after the inoculation of 1×10^6 tumor cells. DDP was given through the hepatic artery (HA) or tail vein (TV). 1054 mg/kg of STS was given iv twice (0 and 5 mins after the initiation of DDP infusion) within a period 1.5 mins. PVL for 5 mins and DDP infusion were initiated simultaneously.

†Calculation of % lifespan was similar to that described in table 1. Mean survival of the untreated controls was 22.5 ± 0.5 days after the tumor cell inoculation. The data were analyzed statistically by Wilcoxon test. NS = not significant. There was no significant difference among Groups B4, C1, and C2.

‡BUN levels were evaluated on Day 4 after the therapy.

§4 of 12 treated rats died of DDP toxicity.

¶Statistical difference from untreated tumored controls by Wilcoxon test, with a *P* value of < 0.01. BUN level of untreated tumored controls was 17.7 ± 2.8 (mean ± SD).

examination was carried out on two rats in each treated group in Experiment 2 on Days 1 and 6 after the chemotherapy.

RESULTS

In Experiment 1, the lifespan of rats treated with TRC (Group A) was statistically longer than that of rats given 5 mg/kg of DDP alone intra-arterially (Group B) or iv (Group C), with a *P* value of < 0.05 or < 0.005, respectively, as shown in table 1. Both groups of rats given TRC and intra-arterial DDP alone showed a similar pattern of weight loss without significant difference (fig 1). In the group given iv DDP alone (Group C), weight loss was less than that in Group A or B on Day 1 after the therapy ($P < 0.01$). If side effects were evaluated according to weight loss, TRC with 20 mg/kg of DDP and treatment with 5 mg/kg of intra-arterial DDP alone show an adverse effect to the same degree. BUN levels increased beyond the normal range, not only in rats treated with 5 mg/kg of intra-arterial DDP alone but also in rats given TRC, when BUN levels were examined preliminarily in Experiment 1 (data not shown).

Experiment 2 was done to observe how the following additional treatments would affect therapeutic efficacy. For TRC, 1054 mg/kg of STS was given twice, and for groups given intra-arterial or iv DDP alone, a dose of 4 mg/kg was tested in addition to the 5-mg/kg dose. Temporary PVL was performed, when DDP was infused intra-arterially, to determine whether the antitumor effect of DDP would be enhanced.

Lifespan, BUN levels, and body weight changes in Experiment 2 are shown in table 2 and figure 2. Among all treated rats, the longest lifespan was observed in the group receiving TRC with PVL (Group A1), with a minimum weight loss and without elevation of BUN levels. Although PVL also resulted in prolongation of the lifespan of rats in groups receiving intra-ar-

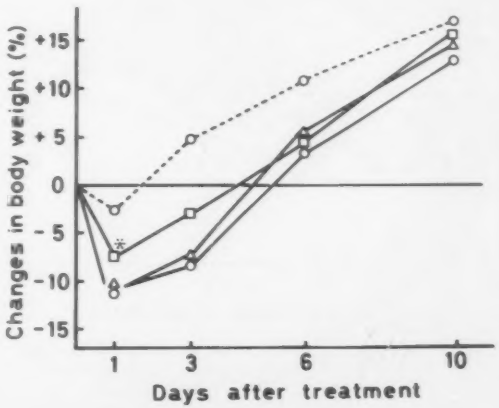

FIGURE 1.—Changes in average body weight of rats after various treatments in Experiment 1. ○———○ = 20 mg/kg of DDP intra-arterially and 1054 mg/kg of STS iv (TRC); △———△ = 5 mg/kg of DDP intra-arterially alone; □———□ = 5 mg/kg of DDP iv alone; and ○----○ = untreated control. Statistical differences ($P < 0.01$) between TRC and each of the other treatments on each day are indicated by an asterisk.

terial DDP alone, at doses of both 5 and 4 mg/kg (Groups B1 and B3), significant weight loss on Days 3, 6, and 10, compared with that in Group A1, and elevation of BUN levels over 80 mg/100 ml of blood were observed; Four of 12 rats in Group B1 died. Considering such severe nephrotoxicity, the data on % lifespan in groups B1 and B3 are not worth evaluating.

Although there was no statistically significant difference between the lifespan of rats treated with TRC without PVL (Group A2) and that of rats treated with 5 mg/kg of intra-arterial DDP without PVL (Group B2), weight loss on Days 3 and 6 and BUN increase in Group B2 were significantly greater.

In the comparison of TRC without PVL (Group A2) with 4 mg/kg of intra-arterial DDP alone without PVL (Group B4), lifespan in the former group was statistically longer than that in the latter, with a P value of

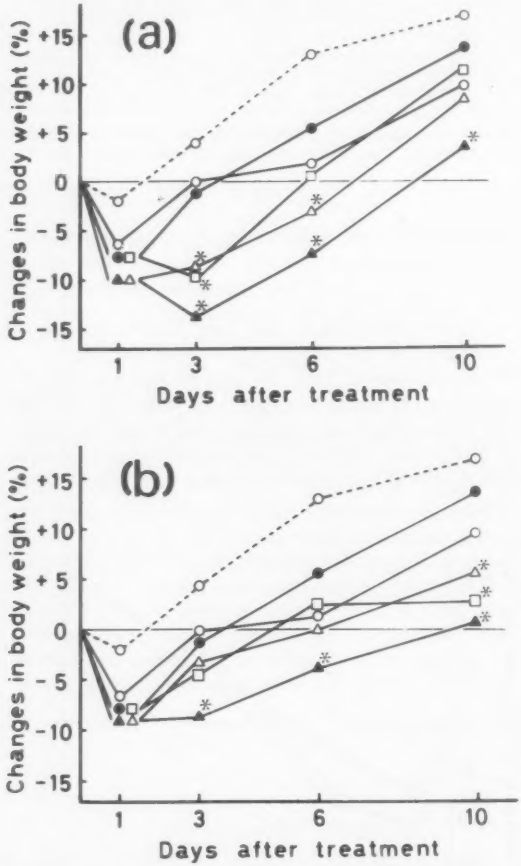

FIGURE 2.—Changes in average body weight of rats after various treatments in Experiment 2. •———• = 20 mg/kg of DDP intra-arterially and 2 doses of 1054 mg/kg of STS iv (TRC) with temporary PVL; ○———○ = 20 mg/kg of DDP intra-arterially and 2 doses of 1054 mg/kg of STS iv; ▲———▲ = intra-arterial DDP with PVL; △———△ = intra-arterial DDP alone; □———□ = iv DDP alone; and ○---○ = untreated control. In (a) and (b), DDP was given in doses of 5 and 4 mg/kg, respectively, when administered intra-arterially or iv alone. Statistical differences ($P < 0.01$) between TRC and PVL and each of the other treatments on each day are indicated by asterisks.

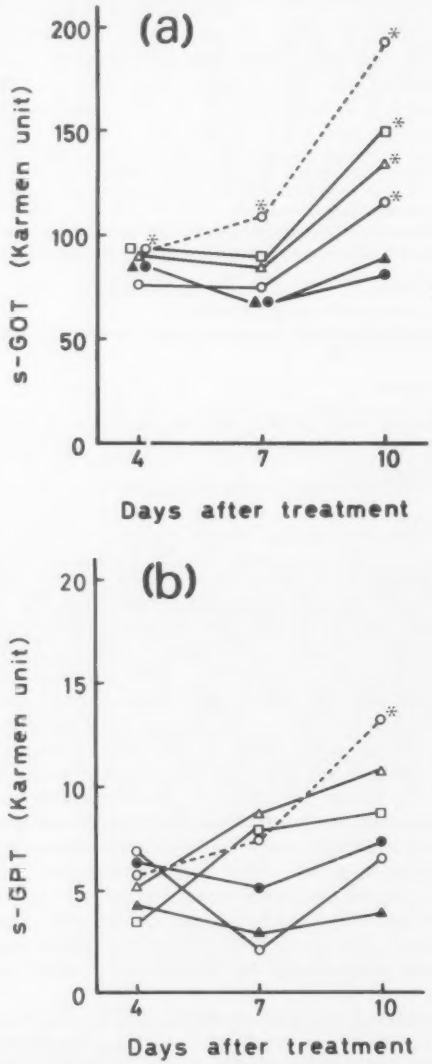

FIGURE 3.—Changes in serum SGOT (a) and SGPT (b) of treated rats in Experiment 2. Symbols are the same as in fig 2. Statistical differences ($P < 0.01$) between untreated nontumored controls and each treated group on each day are indicated by asterisks. SGOT and SGPT levels of untreated nontumored controls were 64.7 ± 18.6 and 6.9 ± 2.5 (n = 7, mean ± SD), respectively.

< 0.1, while both treatments seem to be equitoxic with regard to weight loss and increase in BUN.

Iv treatment with 5 or 4 mg/kg of DDP alone (Groups C1 and C2) showed no significant difference in lifespan compared to treatment with 4 mg/kg of intra-arterial DDP alone without PVL (Group B4). However, BUN levels in these iv treated groups were significantly elevated, although the BUN level in Group B4 was within the normal range. Thus, iv DDP treatments had no significant therapeutic efficacy compared to intra-arterial treatment or TRC.

Figure 3 shows the levels of serum transaminases (SGOT and SGPT) for six rats randomly sampled from each treated group in Experiment 2. Although SGOT and SGPT levels were elevated on Day 10 after the various treatments, except for groups treated with TRC and 5 mg/kg of intra-arterial DDP with PVL, the levels were lower than those in the untreated controls. This seems to indicate that the damage of normal liver cells was not due to drug toxicity, but rather to the invasive growth of tumor cells.

Figure 4 shows representative histologic findings of tumors after chemotherapy. For TRC without PVL, tumor cells were necrosed in the central portion, but survived at the periphery of tumors > 0.8 mm in diameter. There were definite cyst formations containing fibrinous exudate with clear demarcations from the tumor cells on Day 6 (fig 4). However, most tumor cells tended to be viable in small tumors that were less than approximately 0.8 mm in diameter on Day 1 (fig 5). A similar pattern was seen after treatment with intra-arterial DDP alone. When PVL was performed in TRC, cyst formation after tumor cell necrosis was also observed, even in small tumor nodules < 0.8 mm in diameter (fig 6).

DISCUSSION

We have already reported the excellent antitumor effect of TRC on metastatic liver tumors in rats, by evaluating tumor weights on Day 21 after the treatment (4). The tumor weights of rats treated with 20 mg/kg

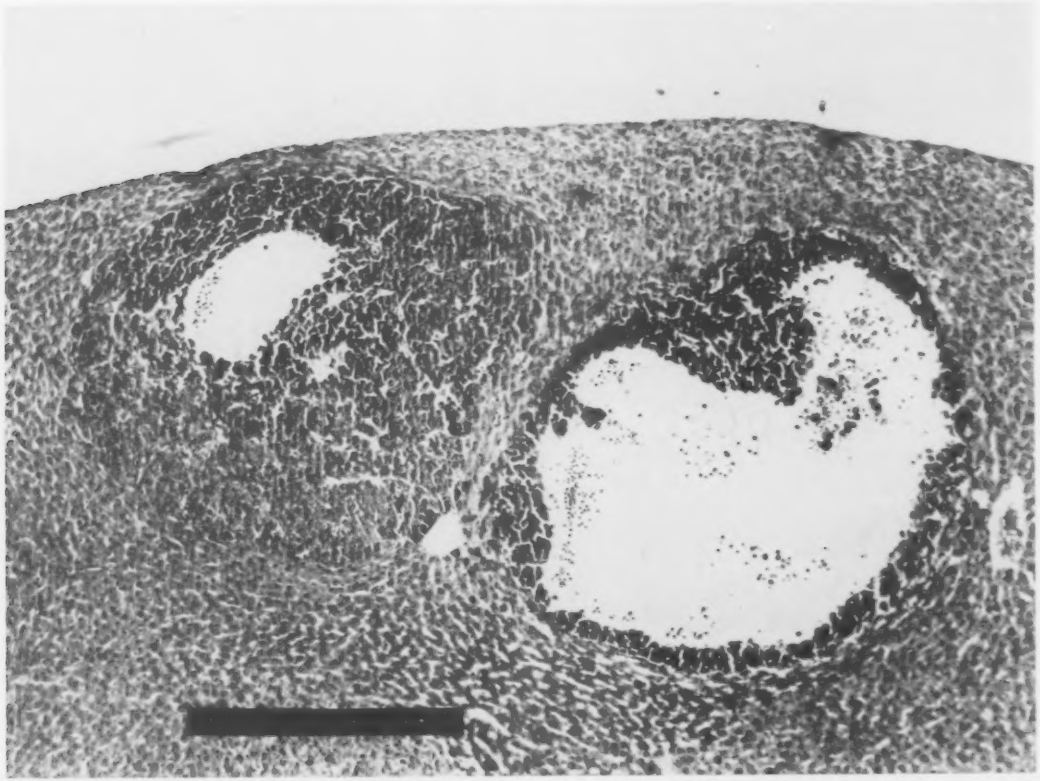

FIGURE 4.—Histologic findings of tumors after TRC with or without temporary PVL in Experiment 2, 6 days after TRC without PVL. Bar represents 1 mm. Hematoxylin and eosin stain, × 40.

of intra-arterial DDP plus 1054 mg/kg of iv STS (TRC), 5 mg/kg of intra-arterial DDP alone, and 5 mg/kg of iv DDP alone were about one-fifth, two-fifths, and three-fifths the tumor weight in untreated controls, respectively. In the present study, rats treated with TRC had the longest lifespan without BUN elevation; however, the lifespan was only 140% that of untreated controls. A similar phenomenon was reported by Cotino and Zwaveling (15), who found that rats treated with continuous intra-arterial 5-FU developed significantly smaller liver tumors than did control animals, but there was no significant difference between the survival times of intra-arterially treated rats and those of controls. In chemotherapy experiments on solid tumor systems, it is difficult to obtain remarkable results by evaluating survival time, because there is an exponential growth of tumor cells. However, considering that our TRC was performed only once on multiple visible tumors 0.5–1.0 mm in diameter and had minimum side effects with regard to body weight change, renal function, and hepatic function compared with other treatments, the therapeutic efficacy of this chemotherapy was outstanding. In small animals such as rats, TRC could be carried out only once, because it is difficult to re-insert a catheter into the hepatic artery, due to adhesion of the liver hilum. If large animals were used, this therapy could be repeatedly applied and a further increase in lifespan may ensue.

In our present study, the question that arises is whether an inhibition of tumor growth was caused by ligation of the hepatic artery (HAL) itself, because the hepatic artery was ligated in order to prevent the inactivation of DDP by influx of STS into the liver via the hepatic artery for TRC or to prevent flush-out of DDP for intra-arterial DDP alone. However, in an experimental study using animals, tumor regression by HAL was only transient (16) and lifespan was not prolonged by HAL (17). Also, in a clinical study, no effect was obtained by HAL with regard to survival (18,19). We also obtained similar results with regard to the ineffectiveness of inhibition of tumor growth (unpublished data). Therefore, the increase in lifespan due to HAL itself

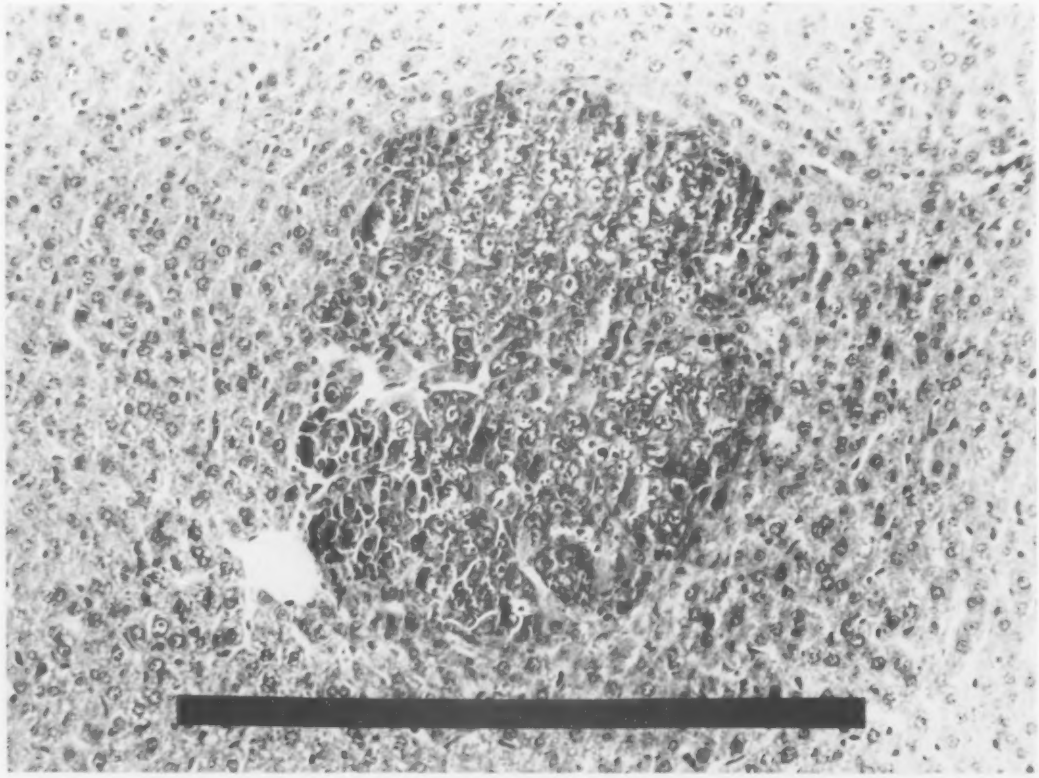

FIGURE 5.—Histologic findings of tumors after TRC with or without temporary PVL in Experiment 2, 1 day after TRC without PVL. Bar represents 1 mm. Hematoxylin and eosin stain, × 100.

seems to be slight, if any, in groups treated with TRC and with intra-arterial DDP alone. Additionally, when comparing the lifespan of animals given TRC with that of the animals given intra-arterial DDP alone, it is clear that the difference between these two treatments does not depend on the effects of HAL itself, because HAL was done in both treatments.

Although tumor tissues of the liver receive their main blood supply from the hepatic artery (8-12), another route of the supply via the portal vein also contributes, particularly in small tumors or at the periphery of large tumors (8,9,20-23). Histologic examination of liver tumors after the chemotherapy showed that the cells survived when diameter of the tumor was less than about 0.8 mm, or in the case of the periphery of large tumors > 0.8 mm in diameter. In our TRC without PVL, DDP seems to be inactivated by STS influxing from the portal vein system, to the level at which DDP cannot irreversibly damage the cells, not only at the site of normal tissues, but also in small tumors or at periphery of large tumors where the blood supply via the hepatic artery is not necessarily predominant. In preliminary experiments, STS was given approximately 1 minute after DDP infusion to assess the therapeutic effect, but improvement of the antitumor effects was slight and protection by STS against DDP toxicity was inadequate (data not shown). Thus, PVL was performed to delay inflow of STS into the liver, and as a result, there was a significant prolongation of lifespan in rats given the TRC. Histologic examination also confirmed that PVL enhanced the therapeutic efficacy in TRC, particularly in tumors less than about 0.8 mm in diameter. There is no clear explanation as to why PVL causes a severe nephrotoxicity in treatment with intra-arterial DDP alone. However, there may be insufficient hydration after the treatment because of intestinal malabsorption due to the epithelial damage by PVL and/or absolute increase of renal flow containing DDP during the PVL.

DDP nephrotoxicity was assessed by checking BUN levels on Day 4 after chemotherapy, on the basis of the finding that BUN reaches a maximum on Days 3-5

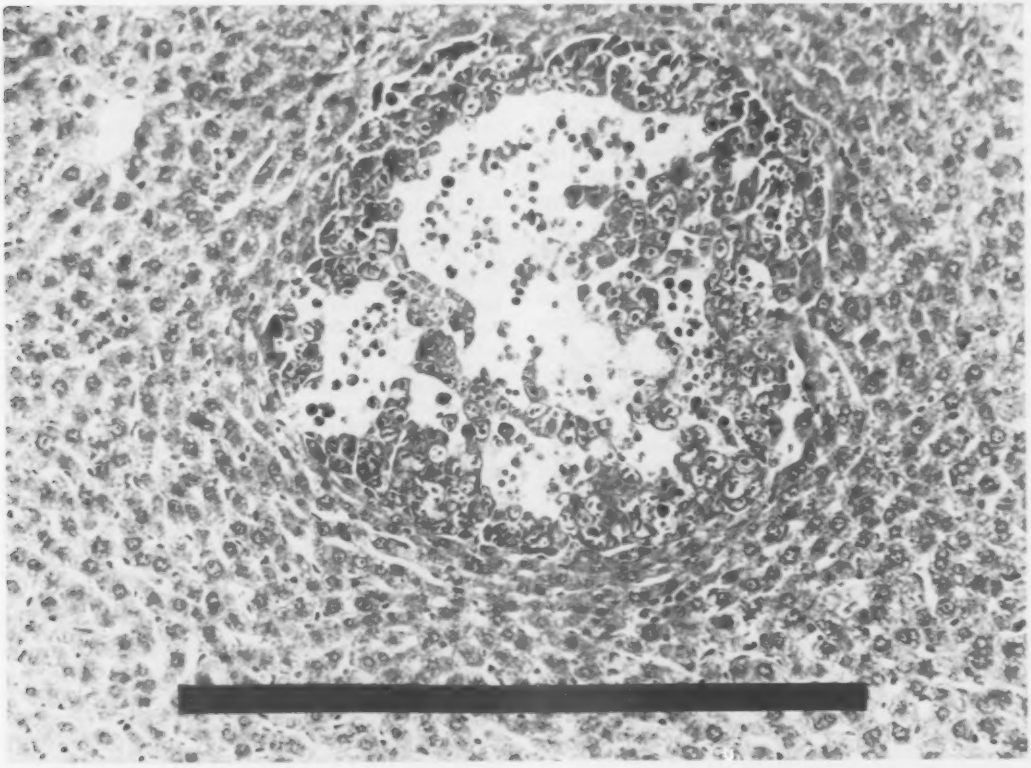

FIGURE 6.—Histologic findings of tumors after TRC with or without temporary PVL in Experiment 2, 1 day after TRC with PVL. Bar represents 1 mm. Hematoxylin and eosin stain, × 100.

after TRC in the bladder tumor system in rats (5,6). Pretorius et al (24) also reported that the peak of BUN levels occurred in dogs on Days 4-5 after DDP administration.

In Experiment 1, STS was given in a dose of 1054 mg/kg, which is a 100-fold molar ratio to 20 mg/kg of DDP. This dose was determined from the results of the antagonistic effect of STS against DDP-induced acute lethal toxicity in mice (25,26) and in our study of TRC on liver tumors in rats (4). Elevation of BUN levels was seen in rats treated with TRC in Experiment 1. It seems that a single administration of STS, in a dose of 1054 mg/kg, was insufficient to completely protect the kidney from the nephrotoxicity induced by a high dose of DDP, probably because of the rapid clearance of STS. Thus, 1054 mg/kg of STS was given twice, at 0 and 5 minutes after the initiation of DDP infusion in Experiment 2, and protection of kidney from DDP nephrotoxicity by STS was attained, except in the two rats treated with TRC without PVL. In pharmacokinetic studies, DDP was considered to be bound to plasma proteins and/or absorbed in some tissue compartments, and then released gradually with a prolonged second phase of plasma clearance curve (27,28). Since a given dose of intra-arterial or iv DDP is usually < LD50, in cases of a single administration the amount of gradually released DDP is negligibly small. In our TRC, because DDP was given in a dose of 20 mg/kg (about 2.7 times the iv LD50 = 7.5 mg/kg in WKA rats), the amount of the gradually released free DDP seems to be sufficient to cause nephrotoxicity after the greater amount of STS has cleared from the plasma. To prevent the exceptional rise of BUN levels in the minority of rats treated with TRC in Experiment 2, an additional administration of STS with proper timing seems necessary. Pharmacokinetics of DDP given in combination with STS are now being investigated.

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Doxorubicin-Induced Skin Ulcer in the Piglet[1,2]

Tsuyoshi Okano, Takao Ohnuma,* Anna Efremidis, and James F. Holland[3,4]

Skin ulceration produced by inadvertently extravasated doxorubicin is characterized by a prolonged course accompanied by severe morbidity, and it has proven to be notoriously difficult to treat. In attempts to identify possible antidotes, 11 different pharmacologic agents were tested using piglets, because their skin is anatomically similar to that of man. Among the agents studied, topical application of DMSO daily for 7 days tended to decrease the maximal diameter and accelerate healing of skin ulcers produced by intradermal doxorubicin. α-Tocopherol appeared to worsen the ulceration. None of the 11 agents studied prevented the development of ulcerations completely. [Cancer Treat Rep 67:1075–1078, 1983]

Among the currently available chemotherapeutic agents, doxorubicin (ADM) has been proven to be one of the most potent, widely used agents for the treatment of human neoplasms (1–3). The known complications of ADM therapy include nausea and vomiting, anorexia, alopecia, mucositis, myelosuppression, cardiomyopathy, and when extravasated, local tissue necrosis (3,4). Skin ulceration following extravasation of ADM is characterized by a prolonged course with slow healing, severe pain, and propensity to invade deep structures such as tendons and joints (5–7). ADM-induced skin ulceration is one of the most distressing side effects. Attempts at preventing ulceration from extravasated ADM in man have included local administration of sodium bicarbonate (8), hydrocortisone sodium succinate (Solu-Cortef) (6), sodium bicarbonate plus dexamethasone (9), and ice packs (10). The efficacy of any method is uncertain.

For the study of ADM skin toxicity, rat (11) and mouse (12) models have been developed. However, the skin of rodents differs from that of man, in that rodents have the panniculus carnosus, a layer of striated muscle located directly below and adjacent to the dermis. This well-vascularized muscle tissue may act as a variant for ADM skin toxicity. Because of the anatomic similarity of pig skin to that of man (13), piglet models were recently developed (14). Details have not been described for this model, however. In an attempt to identify possible counteracting materials for ADM skin toxicity, 11 different agents were tested in this model system.

MATERIALS AND METHODS

Male Yorkshire Albino piglets weighing approximately 8 kg (purchased from Barson's Farm, Hudley, MA) were used in all experiments. Piglets were anesthetized with pentobarbital given ip, and hair was removed from the back with a hair clipper. ADM, which was obtained from Adria Laboratories, Columbus, OH, was dissolved in 0.9% NaCl at graded concentrations, and 1.0 ml of the solution was injected sc or intradermally, using 25-gauge needles. For intradermal ADM injection, the needle was tunneled through the skin for a short distance to prevent leakage of the drug solution which was injected into the dermis, making a bulla. Sc injection was done by placing the needle perpendicular to the skin and injecting at a depth of 5 mm. When the possible antidotes were tested, 0.5 ml of a solution of each agent was given, after changing syringes, through the same needle in situ immediately after the administration of ADM. Control sites received 0.5 ml of 0.9% NaCl solution. DMSO was applied topically at the ADM-injected site for 7 consecutive days. Up to six injection sites were used per piglet.

The following agents were chosen as possible counteragents. All have been reported either to ameliorate ADM

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toxicity in some organ or to interact chemically with ADM: carnitine (γ-trimethyl-ammonium-β-hydroxybutyrate, Bio-Basics International, New York, NY), 50 mg (15); coenzyme Q_{10} (Sigma Chemical Co, St. Louis, MO), 1.6 mg (16); deferoxamine mesylate (Desferyl, CIBA Pharmaceutical Co, Summit, NJ), 125 mg (17); DMSO (Sigma), 3.0 ml per site per day (14,18); dopamine HCl (Intropin, Abbott Laboratories, North Chicago, IL), 20 mg (19); DNA (type V, Sigma), 3.0 mg (20); human serum albumin (Sigma), 100 mg (21); iron dextran (Imferon, Merrell-National Laboratories, Cincinnati, OH), 40 mg (17); isoproterenol HCl (Isuprel, Elkins-Sinn Inc, Cherry Hill, NJ), 40 μg (22,23); sodium bicarbonate (Abbott), 8.4% (8); and α-tocopherol (Sigma), 50 units (18,24).

Skin lesions were recorded two or three times a week, and the largest diameter of ulcerations was measured by calipers, as the parameter of the lesion severity. Piglets were observed for up to 6 weeks. When infection developed before 3 weeks, it was difficult to distinguish ADM-induced ulcers from infection-related ulcers, and such lesions were eliminated from analysis. When infection occurred after 3 weeks of observation, only the data prior to the infection were analyzed.

The investigation was conducted in conformity with all institutional and federal guidelines.

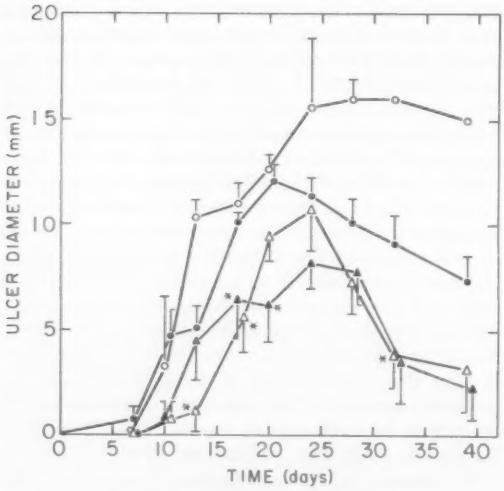

FIGURE 1.—Time course of ADM-induced skin ulcers in concurrent control piglets (●), the effects of topically applied DMSO at the treated sites (▲), and control sites (△) of the same piglets receiving DMSO. Effects of intradermal injection of α-tocopherol (50 units) are also shown (○). Each data point represents an average diameter of 3–19 ulcers, except 1 each for α-tocopherol on Days 32 and 39. The asterisks indicate statistically significant ($P < 0.05$, independent t test) data points, as compared to untreated ulcers of piglets not receiving DMSO. Brackets indicate 1 SEM.

RESULTS

Initially, ADM was injected sc in graded doses to 16 piglets. Ulcerations developed only after administration of > 8 mg/site of ADM, and ulcers were consistently produced only at doses of > 30 mg/site. The sizes of ulcerations were not proportional to the doses given. Large doses of ADM resulted in myelosuppression and mixed infections of the ulcers, which acted as further variables influencing ulcer size and time course.

Intradermally injected ADM (2.0 mg/site) produced skin ulcerations in a predictable manner, although ulcer size varied considerably. A total of 13 piglets were studied. Since our preliminary data and reports by others (14,18) indicated that DMSO had a systemic effect, this agent was studied in four piglets separate from the other agents.

The control peak lesion sizes observed are shown in table 1; 2.0 mg of ADM produced an ulcer with a diameter of 13.7 ± 0.8 mm (SEM, n = 19). Of 11 agents studied, only two, DMSO and α-tocopherol, produced slight changes in ulcer size. When 3 ml of DMSO was applied topically for 7 days, the peak lesion size was decreased to 10.4 ± 1.0 mm ($0.1 > P > 0.05$, n = 5), and the size of the distant control site was decreased to 11.6 ± 1.1 mm ($0.2 > P > 0.1$, n = 7). This change in the distant control site is consistent with the systemic effect of DMSO. In contrast, α-tocopherol made the peak lesion size larger than the size of the controls, ie, 19.3 ± 2.2 mm ($P < 0.05$, n = 3).

The time course of mean size of control ulcers and the effects of DMSO at treatment sites and remote control sites in the same animals are shown in figure 1. DMSO-treated ulcers tended to be smaller and healed faster than

TABLE 1.—Effects of 11 pharmacologic interventions on skin ulcerations induced by 2.0 mg of intradermally injected ADM*

Treatment	n†	Maximal ulcer diameter (mean ± SEM in mm)
ADM only (control)	19	13.7 ± 0.8
ADM + carnitine (50 mg)	3	12.0 ± 2.1
ADM + coenzyme Q_{10} (1.6 mg)	3	14.0 ± 2.3
ADM + deferoxamine mesylate (125 mg)	3	14.7 ± 3.3
ADM only (remote control site in the same animal receiving DMSO)	7	11.6 ± 1.1
ADM + DMSO	5	10.4 ± 1.0
ADM + dopamine HCl (20 mg)	4	11.3 ± 1.9
ADM + DNA type V (3.0 mg)	4	11.3 ± 1.2
ADM + human serum albumin (100 mg)	3	12.7 ± 1.4
ADM + iron dextran (40 mg)	3	11.3 ± 0.9
ADM + isoproterenol HCl (40 μg)	3	12.0 ± 1.2
ADM + 8.4% $NaHCO_3$	4	11.5 ± 1.9
ADM + α-tocopherol (50 units)	3	19.3 ± 2.2‡

*DMSO was applied topically for 7 days. All other agents were injected intradermally just after ADM administration.

†n = No. of lesions in ≥ 2 animals.

‡$P < 0.05$ by independent t test.

those of ADM control ulcers in other piglets. α-Tocopherol tended to produce larger ulcers and prolonged the time required to heal. The other nine agents studied did not modify the peak lesion size and time course of ulceration produced by intradermal ADM.

DISCUSSION

Sc injections of ADM failed to produce consistent ulcerations. This appears to be due to the spread of ADM in the subcutaneous fat tissue. Intradermal injection produced predictable ulcerations in the piglet. These results are consistent with other animal models reported (11,12,25), suggesting that the localization of ADM in the dermis is the critical factor for ADM skin toxicity (25). We find that the maximal ulcer size produced by ADM was variable, even with meticulous efforts to deliver constant amounts of drug at a defined depth of the skin.

In our study, all 11 agents failed to prevent the development of ulceration; only DMSO showed some preventive activity against ADM skin ulcers. Desai and Teres (14) reported that topical application of DMSO completely prevented the development of ulceration, not only at the local treated site, but also at the distant control site in rats and piglets. Svingen et al (18) reported that using the rat model and a similar dose schedule of DMSO, the agent reduced the size of ulceration but could not prevent the development of ulcer completely. Our results in piglets are consistent with the findings of Svingen et al. The effect of more frequent or prolonged application would seem to be the appropriate question in designing subsequent studies.

α-Tocopherol increased the peak lesion size significantly. The reasons for this unexpected observation are unclear. The pathogenesis of ADM skin ulceration is reported to be due to the local superoxide formation. It is of interest that DMSO and α-tocopherol, both considered to be superoxide scavengers, reacted in opposite manners. α-Tocopherol, dissolved in DMSO and applied topically for 2-7 days, was found to produce decreases in ADM skin ulcers in rats (18); however, intradermal α-tocopherol in mice was reported to worsen the lesions (23). In our study, DMSO was given for 7 days, but α-tocopherol was given only once and the dose might not have been sufficiently high. Since α-tocopherol was given as an oil solution, it is possible that the oil might have acted as a retainer of ADM at the injected site and sustained high local concentration of ADM, causing the larger skin ulcerations.

Dorr and Alberts (22,23) reported that isoproterenol HCl and propranolol HCl reduced the ulcer size and shortened the time required to heal in rats. In our study, we used the dose of isoproterenol HCl that was proportionally similar to that of ADM, but it did not modify the ADM ulcer in piglets. It is possible that this difference is related to the difference in species. Among the agents clinically given, glucocorticoids had been tested in rats or mice and were shown to have no preventive activity against the development of ADM ulcers (12,26); therefore, we did not test them.

None of the 11 agents studied were able to prevent the ADM skin ulcerations completely. This means either that they were not active or that the doses were too low. The latter is unlikely, however, since we used the dose of each agent reported to be pharmacologically active. The activity of DMSO against ADM-induced ulcers is of interest. Clinical testing of DMSO or related compounds for the prevention of ADM skin ulcers in man is warranted.

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Specificity of Antisera Produced Against Mitomycin C[1,2]

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The specificity of antisera produced in rabbits for use in mitomycin C (MMC) enzyme immunoassay has been examined employing competitive experiments using several mitomycin analogs and the chemically or biologically degraded preparations of MMC. These studies demonstrate that the antiserum distinguished alterations in the chemical structure of the molecule, showing decreased immunoreactivity with mitomycin A (7.8%) and B (0.78%). On the other hand, porfiromycin and acetyl MMC (Ac-MMC), which commonly possess the substituted groups (methyl and acetyl groups, respectively) at the aziridine ring, showed enhanced reactivity with the antiserum (about two times and ten times as compared to the parent MMC, respectively), suggesting that the antigen used for antibody production was the MMC acylated at the imino group of the aziridine ring. The values of the chemically or biologically degraded preparations of MMC quantified by this enzyme immunoassay were in good agreement with those of the remaining nonreacted MMC measured spectrophotometrically, thus indicating that the anti-MMC antiserum hardly cross-reacted with these degradation products. [Cancer Treat Rep 67:1079–1084, 1983]

The antitumor antibiotics mitomycin A (MMA) and B (MMB) from *Streptomyces caespitosus* exhibited broad and potent antitumor activities as well as antimicrobial activities (1). Thereafter, mitomycin C (MMC) was isolated from the same strain by Wakaki et al (2) and has been clinically used for the treatment of a variety of human cancers (3,4). MMC probably induces its antitumor effects, after being bioreductively activated, by covalent binding to cellular DNA (5) and cross-linking between the complementary strands of the nucleic acids (6,7).

We recently developed an enzyme immuncassay (EIA) for MMC that proved to be 25 times more sensitive than previously reported microbiologic assays (8). Evaluation of the specificity of the immunoassay will make it valid for use in pharmacologic and toxicologic studies of MMC. Since antiserum was prepared with an MMC-bovine serum albumin conjugate, a study of the specificity of the antibody raised in rabbits was undertaken using MMC analogs and the chemically or biologically degraded preparations of the drug.

MATERIALS AND METHODS

Materials.—MMA, MMB, and MMC were provided by Dr. K. Kishibe of Kyowa Hakko Kogyo Co, Ltd, Tokyo, Japan. Acetyl MMC (Ac-MMC) and porfiromycin were prepared according to the method of Matsui et al (9).

Chemical derivatives produced by phosphorylation of MMC.—MMC derivatives were prepared by using a slight modification of the method of Tomasz and Lipman (10). MMC (0.61 mg; 1.83 μmols) was incubated in 1.5 ml of 0.34 M acid phosphate solution, pH 3.0, at 25°C for 24 hrs with stirring. The reaction mixture was adjusted to pH 6.9 by adding 1 N NaOH. The precipitate formed was separated by centrifugation and redissolved in a limited volume (300 μl) of a 6 M urea solution. It was then combined with the supernatant previously separated, and the mixture was extensively diluted with 50 mM phosphate buffer, pH 6.9, for use in the cross-reactivity experiments.

Reduction of MMC.—MMC (38.9 μg; 0.116 μmol) in 50 μl of 0.34 M sodium phosphate, pH 7.0, was de-aerated by

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bubbling nitrogen gas for 5 mins; 1 μl of 1 M sodium borohydride (1 μmol) was then added at room temperature. After a 10-min incubation, the mixture was diluted with Buffer A (0.06 M sodium phosphate, pH 7.4, containing 0.01 M EDTA and 0.1% bovine serum albumin) in a total volume of 5.0 ml and was used for EIA determination.

Metabolism of MMC.—For the study of MMC metabolism by rat tissues, Wistar rats (weighing about 150 g) were killed by cervical dislocation. Each tissue was quickly obtained, rinsed, blotted, weighed, cut into small cubes, and homogenized with 5 vols of ice-cold 50 mM phosphate buffer, pH 7.0, with five-times strokes using a glass homogenizer under an ice bath. MMC (38.4 μg; 0.115 μmol) in 100 μl of 50 mM phosphate buffer, pH 7.0, was added to 400 μl of fresh tissue homogenate, and the mixture was incubated at 37°C in the presence [94.6 μg (0.114 μmol) or 473 μg (0.568 μmol)] or absence of NADPH. After a 1-hr incubation, the reaction was stopped by adding 4.5 ml of ethanol, and the mixture was centrifuged at 2200 rpm for 15 mins. The supernatant, 4.0 ml, was entirely dried by flashing nitrogen at 30°C, and the residue was redissolved in 400 μl of Buffer A for use in the EIA determination.

EIA.—Competitive antibody-binding experiments for MMC analogs or its degraded preparations were performed by adding known concentrations of the drug to a solution containing antiserum plus β-galactosidase-labeled MMC (MMC-β-Gal) and by measuring the amount of labeled drug bound by antibody as previously reported (8). The immunoreactivity was estimated as the amount of MMC analogs or the degraded preparations required to produce 50% inhibition of bound MMC-β-Gal.

RESULTS AND DISCUSSION

Natural mitomycin (A, B, and C) and its chemical derivatives, porfiromycin and Ac-MMC, were prepared and used to investigate the specificity of anti-MMC antibody. The specificity was determined by measuring the displacement of bound MMC-β-Gal by the mitomycin analogs. Calibration curves showing the relationship between concentrations of unlabeled agents and the percentage of bound MMC-β-Gal were plotted (fig 1). The anti-MMC antibody showed only 7.8% cross-reaction with MMA and 0.78% with MMB, defined as the amount of each drug required for 50% binding inhibition. On the other hand, porfiromycin and Ac-MMC effected slightly greater displacement of MMC-β-Gal than MMC, with 227% and 1035% cross-reaction, respectively.

Competition of MMC analogs with MMC-β-Gal for antibody recognition provides evidence for the antibody recognition sites of antiserum prepared using MMC. Among the analogs tested (fig 2), the substitution of a methoxy group at the 7-position (in case of MMA) effectively eliminated antibody recognition. Further alterations in the configuration of the methylurethane group and in the substitution of a hydroxy group and methyl group at the 9_a-position and the aziridine moiety, respectively, producing MMB led to much lower reactivity with the antibody. Since the immunodominant groups of a hapten are usually apart from the site of conjugation with the carrier protein (11), the site of conjugation was probably not at the amino group at the 7-position of MMC. Furthermore, the fact that migration of the methyl group or acetyl group on the aziridine moiety producing porfiromycin or Ac-

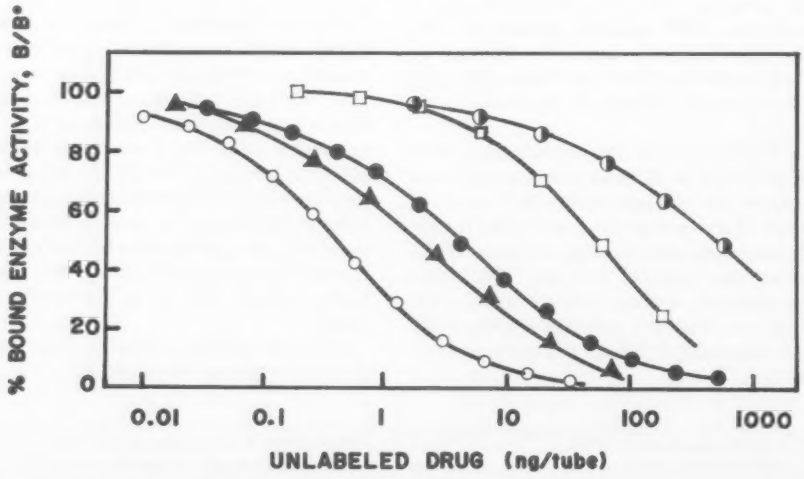
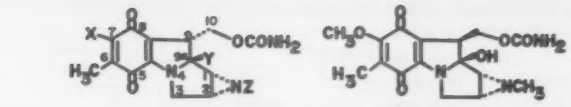


FIGURE 1.—Cross-reactivity of some mitomycin analogs with anti-MMC serum. Curves show the amount (%) of bound enzyme activity for various doses of MMC or its analogs (B) as a ratio of that bound using the MMC-β-Gal alone (B°). ○ = Ac-MMC; ▲ = porfiromycin; ● = MMC; □ = MMA; and ◑ = MMB.



	X	Y	Z
Mitomycin A	CH_3O	CH_3O	H
Mitomycin C	NH_2	CH_3O	H
Porfiromycin	NH_2	CH_3O	CH_3
Acetyl-mitomycin C	NH_2	CH_3O	$COCH_3$

FIGURE 2.—Structures of MMC and some mitomycin analogs.

MMC caused a twofold or a tenfold increase in efficiency of competition for MMC antibody, respectively, indicates that the antiserum clearly recognizes the sites of the substituted methyl or acetyl group on the aziridine ring. It would therefore be concluded that the site for carbodiimide-mediated MMC conjugation to the thiolated bovine serum albumin via a cross-linker, *N*-maleoyl aminobutyric acid, has been the imino group of the aziridine ring as predicted in the previous paper (8).

MMC is known to be the prototype of a class of antitumor drugs, the bioreductive alkylating agents, which required metabolic reduction to form a species capable of alkylating critical cellular macromolecules (12). Schwartz et al (12,13) reported that MMC was metabolized by rat liver homogenates and the metabolism was proportional to loss of biologic potency. A highly sensitive EIA of MMC is considered to be an extremely useful tool for elucidating the possible metabolic pathway and conditions for MMC activation. Thus, evaluation of the cross-reactions of anti-MMC antibody to the metabolites of MMC by several tissue homogenates was made. Known concentrations of MMC were incubated with a fixed amount of freshly prepared tissue homogenates under several conditions. After tissue debris was removed from the test samples, the supernatant fractions were estimated as the concentrations of MMC by the EIA. Typical calibration curves for the quantification of MMC incubated with rat kidney homogenates are shown in figure 3 as a function of the initial values of added MMC. Judging from the values of a 50% binding inhibition, MMC was reduced by incubation in the presence of equimolar or fivefold molar NADPH for 1 hr, to the level of 14% or

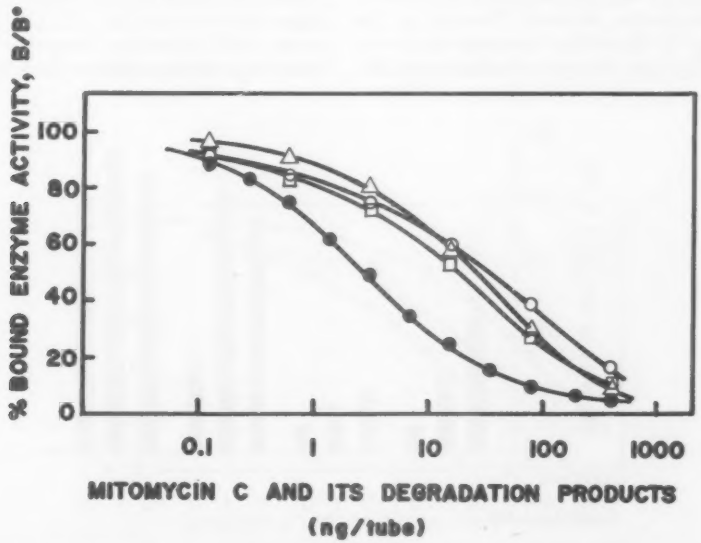


FIGURE 3.—Indication of MMC degradation by rat kidney homogenate. MMC (38.4 μg) was incubated with rat kidney homogenate (wet weight, 80 mg) at 37°C for 1 hr, in the presence of equimolar (△) or 5-fold molar NADPH (○) to the amounts of the drug, or in the absence of NADPH (□). As a control, the reaction of MMC with ethanol-treated kidney homogenate was carried out in the same manner (●). % bound enzyme activity (B/B°), expressed in the same manner as in fig 1, is given as a function of the initial values of MMC at the beginning of the incubation.

TABLE 1.—Comparison of assay methods in the measurement of the metabolism of MMC by rat liver homogenates*

Incubation time (mins)	Initial contents		Change in MMC concentration (Δ μg/ml)†	
	Liver (mg)	MMC (μg/ml)	A	B
60	0	78.6	0	0
5	80	78.6	-50.3	-39.3
30	80	78.6	-70.7	-66.8
60	80	78.6	-72.8	-71.9
240	80	78.6	-76.2	-72.3

* MMC (78.6 μg) and liver homogenate were incubated in 50 mM phosphate buffer, pH 7.0. MMC was measured spectrophotometrically at 363 nm and by the EIA.
†A = spectrophotometrically; B = by the EIA.

7.5% of the initial value, while a 19.4% recovery was observed in the absence of NADPH. The metabolizing capacity disappeared by heating the homogenates at 100°C for 10 mins. These results strongly suggest that MMC might be metabolized in the homogenates, and more readily so in the presence of NADPH.

Other tissue homogenates of rats were also tested for its metabolizing capacity of MMC (fig 4), and it was found that MMC was readily metabolized in the liver and kidney but rather slowly in the brain and stomach. Degradation of the drug was also marked with increasing quantities of NADPH. These organs, the liver in particular, may be the main site of MMC degradation. Therefore, a more detailed experiment was carried out with rat liver homogenates using three metabolic systems, ie, in nitrogen, oxygen, and carbon monoxide atmosphere. As shown in figure 5, MMC was progressively degraded with time by any homogenates prepared. However, at the rather early stage of incubation, the metabolism was slightly inhibited by either oxygen or carbon monoxide. A striking stimulation of MMC metabolism by NADPH was also observed in all of the metabolic systems. These results indicate that metabolism depends on phosphonicotinamide adenine nucleotides and their associated dehydrogenases, and this is entirely consistent with previous findings by others (14,15) using spectrophotometry or microbiologic assays for MMC (2,16,17). The metabolism of MMC was usually measured by changes in absorption at 363 nm. Thus, the values determined spectrophotometrically were compared with the EIA determinations in several experiments. The results shown in table 1 indicate that the two methods of measurement were in good agreement.

Experiments were also designed to measure the cross-reactivity of anti-MMC antibody with the chemically degraded preparations of MMC (fig 6). MMC was alkylated by acid phosphate (10) or reduced by sodium borohydride (spectrophotometrically, with 17% or 27% of the nonreacted MMC remaining, respectively); preparations reacted with the anti-MMC antibody by 12.3% or 31.7% of

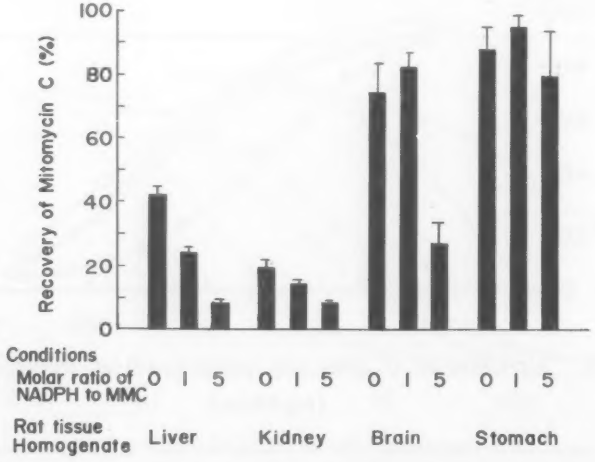


FIGURE 4.—Recovery of MMC after incubation with rat tissue homogenates. Each tissue homogenate was similarly prepared and 80 mg (wet weight) of each was used for the MMC degradation reaction (37°C, 1 hr) in the presence or absence of NADPH.

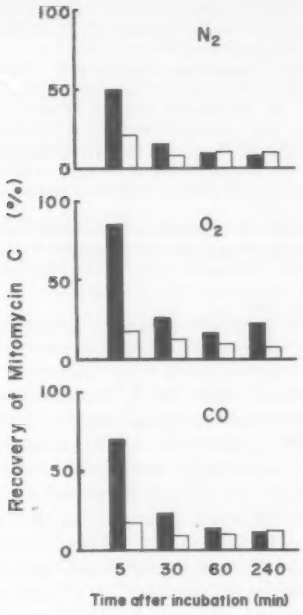


FIGURE 5.—Time dependence of the MMC degradation by rat liver homogenates. 3 types of rat liver homogenates were prepared using 50 mM phosphate buffers (pH 7.0) saturated with nitrogen, oxygen, and carbon monoxide, respectively. Incubation of MMC (235.8 μg) with each homogenate (wet weight, 480 mg) in a total volume of 3.0 ml was carried out in air at 37°C in the presence (1.5 mg) (□) or absence (■) of NADPH, and aliquots of 500 μl were periodically withdrawn from the reaction mixture followed by measurement of MMC concentrations by the EIA.

the initial value, respectively, thus indicating almost no cross-reactivity of either chemically degraded MMC with the antibody.

On the basis of the cross-reactivity experiments described here, it would appear that anti-MMC serum is specific to intact MMC, but not to its metabolites or bioreductively activated MMC, thus suggesting that the EIA of MMC has the advantages of detecting a minute amount of MMC in physiologic conditions hitherto impossible spectrophotometrically or by microbiologic assays for clinical investigators. Although the anti-MMC serum was found to show the rather higher reactivity with porfiromycin and Ac-MMC than with MMC, these analogs may not interfere with the determination of MMC by this EIA, since MMC chemotherapy has not been undertaken in combination with porfiromycin, and also no evidence of Ac-MMC as an MMC metabolite has been available.

Further, a possible development of EIA for sensitive quantification of porfiromycin using the reagents of anti-MMC serum and MMC-β-Gal has been suggested in the present study, and the evidence will be reported elsewhere.

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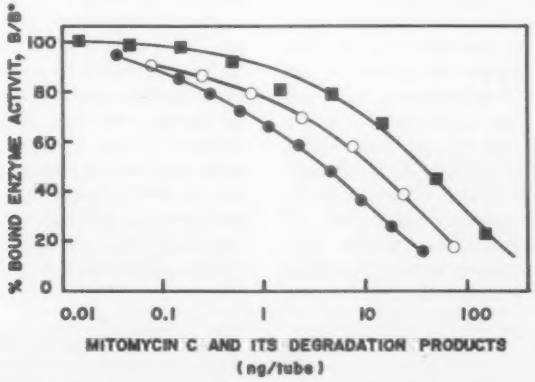

FIGURE 6.—EIA of chemically degraded preparations of MMC. % bound enzyme activity (B/B°) is given as a function of the initial values of MMC at the beginning of the degradation reaction. ● = MMC; ■ = preparation of phosphoalkylated MMC; and ○ = sodium borohydride-reduced preparation of MMC.

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Pharmacokinetics of Ip Cisplatin in Refractory Ovarian Carcinoma[1,2]

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Four patients with small residual ovarian carcinoma following treatment with cisplatin, doxorubicin, and cyclophosphamide have subsequently received 57 courses of ip cisplatin. Cisplatin (120–270 mg in 2 L of Ringer's lactate) was administered via Tenckhoff catheter, with a dwell time of 15–20 mins. Courses were given weekly for 12 weeks, with response documented by laparoscopy or laparotomy prior to and following the trial. With a dwell time of 20 mins, 75% ± 5% (mean ± SD) of platinum was recovered. With 120 mg of cisplatin and a dwell time of 20 mins, total plasma platinum peaked at 1.23 ± 0.42 μg/ml and by 8 hrs decreased to 0.67 ± 0.12 μg/ml. Filterable (non-protein-bound) platinum peaked at 0.73 ± 0.21 μg/ml and by 8 hrs fell to 0.03 μg/ml. Excretion rate paralleled the filterable plasma curve, peaking at 40 mins; 30% ± 7% of absorbed drug was recovered in urine within 24 hrs. Renal clearance of filterable platinum was 106 ± 20 ml/min. Creatinine clearance was 76 ± 7 ml/min. Three responses, one complete and two partial, were noted. Zero to two episodes of vomiting occurred in each course. One patient had a creatinine clearance decrease to 40 ml/min, one had two episodes of thrombocytopenia, and one had mild abdominal pain with a cisplatin dose of ≥ 210 mg. No neurotoxicity, catheter infection, or peritonitis was encountered. [Cancer Treat Rep 67:1085–1092, 1983]

Cisplatin has significant activity against human ovarian carcinoma (1–5). In ovarian (4) and testicular (6) carcinomas, in animal tumor systems (7), and in tissue culture (8), the activity of cisplatin has been shown to be dose-dependent. A recent study in dogs has shown that the level of cisplatin in the tissues lining the peritoneal cavity can be increased by a factor of 2.5–8 by administering the drug ip rather than iv (9). Systemic toxicity was unaffected by mode of administration, and chemical peritonitis was not seen if the concentration of cisplatin was < 55 μg/ml. Since ip cisplatin increases intraperitoneal tissue levels without increasing toxicity, and since cisplatin activity is dose-dependent, we believed that ip cisplatin would have increased activity against ovarian carcinoma confined to the peritoneal cavity. Reported here are the preliminary results and pharmacokinetics of ip cisplatin in patients with ovarian carcinoma who have failed systemic chemotherapy with cisplatin, doxorubicin, and cyclophosphamide.

MATERIALS AND METHODS

Eligible patients had small (< 1 cm) residual ovarian carcinoma following multiple-agent chemotherapy, including cisplatin. All patients had stage III or IV ovarian carcinoma, and all had at least an initial response to combination chemotherapy. Two patients had persistent disease at second-look laparotomy: one had progressive disease and had secondary cytoreductive surgery, and one had a negative second-look laparotomy but recurrence was noted 9 months later. Adequate hematologic, renal, and hepatic functions (as defined by initial wbc count > 3000/mm^3; platelet count > 100,000/mm^3; creatinine clearance > 50 ml/min; and normal SGOT, SGPT, and bilirubin) were required for admission to the protocol. The following conditions excluded patients from this trial: extensive abdominal adhesions; ovarian carcinoma in the lung, parenchyma of the liver, or subcutaneous tissue; or weakness secondary to neurotoxicity of iv cisplat-

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in. Patients eligible for the trial gave informed consent and had placement of permanent Tenckhoff peritoneal dialysis catheters. Two patients had catheters placed at laparotomy for second-look or secondary debulking, and two had open laparoscopies specifically to place the catheter. Patency and sterility of the Tenckhoff catheter was assured by irrigation and aseptic technique as per an established renal dialysis protocol (10). To allow patients to recover from surgery, the first course of ip cisplatin was given 7–10 days postoperatively.

Courses of ip cisplatin were given weekly for 12 weeks and were followed by open laparoscopy or laparotomy for assessment of response. Prior to each course creatinine clearance, wbc count, platelet count, serum magnesium, calcium, electrolytes, and hemoglobin were measured. Patients were admitted in the evening and were hydrated overnight with Ringer's lactate. If hematologic and renal indices were adequate, patients were premedicated with lorazepam (2–4 mg iv) and thiethylperazine (10 mg im) 30 mins prior to ip therapy (11). Two liters of Ringer's lactate (prerinse) was allowed to run into the peritoneal cavity over 10–12 mins and then was allowed to drain for 7 mins. The iv tubing was removed from the bag and was inserted into a 2-L vacuum bottle. The patient's position was changed and the vacuum drainage continued for an additional 5 mins. If < 1400 ml of fluid was obtained from the prerinse, steps to improve catheter function were taken prior to continuing with therapy. Repeated flushing of the catheter, change in the patient's position, and evacuation of colon were found to be helpful. If all efforts failed, the catheter was removed and replaced. No attempts at repositioning catheters were made. If at least 1400 ml of Ringer's lactate was recovered, the Ringer's lactate containing the cisplatin was allowed to flow into the abdominal cavity in a manner analogous to the prerinse. The patient's position was changed every 2 mins to facilitate uniform ip exposure to the drug. Cisplatin remained in the abdominal cavity for either 15 or 20 mins measured from the time infusion began to the time fluid removal began (ie, dwell time). The solution containing cisplatin was removed by gravity drainage for 7 mins and then by vacuum for 5 mins. A third 2-L bag of Ringer's lactate (postrinse) was allowed to run into and then out of the peritoneal cavity in a manner analogous to the prerinse. The Tenckhoff catheter was flushed with 12 ml of sterile saline plus 2000 units of heparin and was then capped. Patients received lorazepam (2 mg sublingual every hr for 4 hrs) then lorazepam (1 mg sublingual every hr for 2 hrs) plus thiethylperazine (10 mg im every 4 hrs) for nausea. Hydration was continued for 6 hrs after ip drug administration and patients were discharged on the afternoon of therapy. The dose of cisplatin was initially 120 mg and was increased each week by 30 mg until either marrow, renal, or local toxicity was encountered. If the absolute granulocyte count, platelet count, or creatinine clearance was rapidly falling, regardless of the absolute numbers, the dose of cisplatin was decreased to 60 mg. If the platelet count fell to < 75,000/mm^3, the neutrophil count to < 750/mm^3, or the creatinine clearance to < 40 ml/min, chemotherapy was withheld and the Tenckhoff catheter was irrigated with Ringer's lactate only. Ip cisplatin was discontinued if a complete response was documented by laparotomy, if disease progression occurred, or if drug toxicity precluded administration of cisplatin for > 2 weeks.

In 32 of 57 courses, ^{195m}Pt-labeled cisplatin was used as a tracer to measure platinum levels (12). The labeled cisplatin was obtained from the Oak Ridge National Laboratories and was added to the second Ringer's lactate bag along with the nonradioactive cisplatin. After mixing, five 1-ml aliquots were removed and placed in gamma-counting vials. The volume of fluid obtained from the peritoneal cavity was measured and five 1-ml aliquots were obtained. Aliquots of fluids were counted using a Beckman gamma counter until a 2 sigma counting error was < 2%. On 28 occasions, 2 μCi of label was added and platinum levels in peritoneal effluent only were measured. On four occasions, 250–400 μCi of labeled cisplatin was added to 120 mg of cisplatin and administered in 2 L of Ringer's lactate, with a dwell time of 20 mins. On these four occasions, levels of filterable and total plasma platinum and urine platinum were measured. During pharmacokinetic studies, patients had 3-way Foley catheters so that 50 ml of sterile 0.9% sodium chloride could be used to irrigate the bladder at the end of each collection period. The volume of urine for each collection period was measured and two aliquots were obtained. Blood samples were placed immediately in heparinized tubes and then placed on ice. Separation of filterable from total plasma platinum was done by centrifugation on Amicon CF50A cones by the method previously described by Bannister et al (13). Duplicate 1-ml specimens of plasma and plasma filtrate were placed in counting vials and were counted on the gamma counter.

Clearance of filterable platinum was determined by dividing the total drug recovered in the urine during the first 8 hrs by the area under the filterable platinum curve from 0 to 8 hrs (14). Curve fitting for determination of the slope of the exponential portion of the plasma decay curve and the slope of the ratio of filterable to total plasma platinum was done by the least-squares method. A complete response was defined as no evidence of carcinoma on laparoscopic-directed biopsies or peritoneal cytology. A partial response was defined as a 50% reduction in the product of two dimensions of a tumor nodule noted at laparoscopy.

RESULTS

Figure 1 shows the mean plasma platinum concentration following 120 mg of cisplatin administered ip, with a dwell time of 20 mins. Highest mean total plasma plati-

num level occurred 42 mins after beginning infusion and was 1.23 ± 0.42 μg/ml (mean ± SD). The total platinum remained elevated throughout the period of observation and at 10 hrs had decreased to 0.55 ± 0.08 μg/ml. Mean filterable, non-protein-bound platinum peaked at 42 mins at 0.73 ± 0.21 μg/ml and then rapidly fell so that by 10 hrs the level was 0.02 μg/ml. The exponential decay phase of the filterable platinum curve (between 42 and 120 mins) has a mean slope of 0.85 ± 0.32 hrs^{-1}. Prior to 42 mins the filterable to total platinum ratio was 0.70 ± 0.04. Between 42 and 360 mins the ratio decreased exponentially, with a slope of 1.35 hrs^{-1} [correlation coefficient (r^2) = 0.995]. Between 360 and 600 mins the ratio was 0.04. The renal excretion rate of platinum peaked at 50 mins at 83 ± 32 μg/min and rapidly fell so that by 10 hrs the excretion rate was 1.9 ± 0.3 μg/min.

Table 1 presents a summary of the pharmacokinetic studies on each of the four patients. Peak plasma levels were reached between 34 and 54 mins after the beginning of infusion. The absolute value of the peak total plasma platinum varied between 0.83 and 1.59 μg/ml. Peak filterable plasma platinum varied between 0.5 and 0.95 μg/ml and was 42–72 times lower than the lowest platinum level within the peritoneal effluent. The renal clearance of filterable platinum varied between 94 and 133 ml/min, slightly more than the creatinine clearance (mean, 76 ± 7 ml/min). The percent of absorbed drug recovered in the urine in 24 hours varied between 25% and 40%, with a mean 30% ± 7%. the amount of platinum absorbed from the peritoneal cavity was much higher for one patient (No. 3, at 43.95 mg) than for the remaining three patients (mean, 27 mg). For the 32 courses in which absorption was calculated, recovery of platinum in the peritoneal effluent was 75% ± 5% (N = 14, dwell, 20 mins) and 78% ± 6% (N = 18, dwell, 15 mins). The mean dose absorbed was 20 mg/m^2/week. A synopsis of each patient's course is compiled in table 2. Three responses, one complete and two partial, were noted. Three patients received 12 courses of ip chemotherapy and one (Patient 1) received 21 courses. Patient 3, who had a complete response, had peritoneal studding and positive pelvic nodes and had response documented by 11 negative cytologic examinations and biopsy at laparoscopy. She subsequently received whole-abdominal radiation therapy to eradicate nodal disease. Patient 4, who had progression on ip cisplatin, had sarcomatoid elements in a grade 3 ovarian carcinoma and died in November 1982. Patient 1 received 12 courses of ip cisplatin, developed thrombocyto-

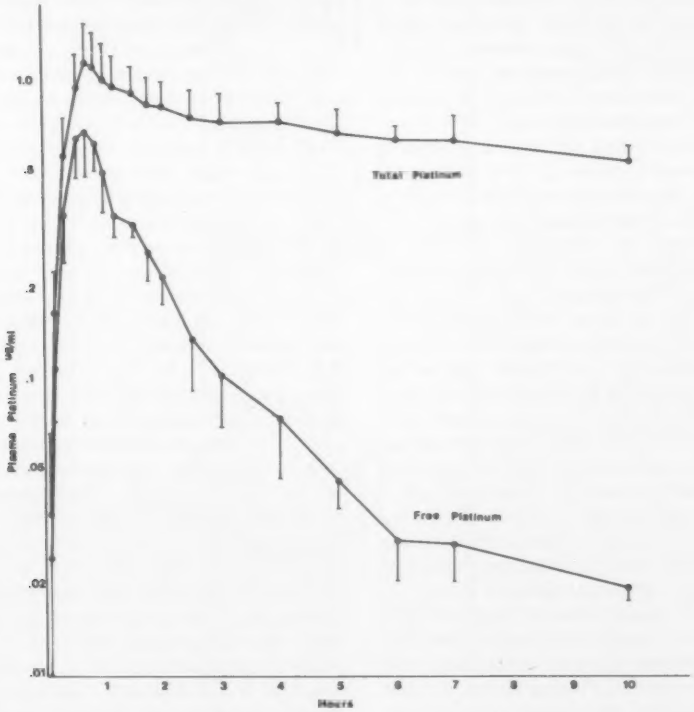

FIGURE 1.—Semilogarithmic plot of mean total and free platinum ± SD vs time following ip administration of 120 mg of cisplatin in 2 L of Ringer's lactate, with a dwell time of 20 mins.

TABLE 1.—Filterable and total plasma platinum, renal excretion, and systemic absorption following ip administration of 120 mg of cisplatin in 2 L of Ringer's lactate, with a dwell time of 20 mins

Patient No.	Total plasma platinum (μg/ml)		Filterable plasma platinum (μg/ml)		Renal platinum excretion rate (μg/min)		Renal clearance of filterable platinum (ml/min)	Creatinine clearance (ml/min)	Platinum absorbed (mg)	% absorbed platinum excreted in 24 hrs
	Peak	8 hrs	Peak	8 hrs	Peak	8 hrs				
1	1.59	0.77	0.95	0.02	117	2.6	133	71	27.2	40
2	0.83	0.57	0.51	0.03	61	2.3	89	71	27.7	27
3	1.59	0.78	0.86	0.05	99	3.2	109	77	44.0	25
4	0.91	0.55	0.60	0.05	54	1.7	94	85	27.0	26
Mean ± SD	1.23 ± 0.42	0.67 ± 0.12	0.73 ± 0.21	0.03	83 ± 30	2.5 ± 0.6	106 ± 20	76 ± 7	31.4 ± 0.8	30 ± 7

penia (platelet count, 40,000/mm^3), and had a partial response. She then received another nine courses and was removed from the study when she developed thrombocytopenia a second time. She subsequently received ip *Corynebacterium parvum* followed by whole-abdominal radiation therapy. Patient 2 received 12 courses of ip cisplatin, had a decrease in creatinine clearance to 40 ml/min, and was subsequently treated with whole-abdominal radiation therapy. The responders (Patients 1, 2, and 3) are all currently (June 1983) without evidence of disease. All patients had none to two episodes of vomiting per course, and one had mild abdominal pain with a cisplatin dose > 210 mg. No neurotoxicity, catheter infection, or peritonitis was noted.

DISCUSSION

This protocol was designed to study the pharmacology of ip cisplatin in patients with small residual ovarian carcinoma. Control of large disease (> 1 cm) and ascites was not attempted. Ringer's lactate was chosen as the dialysate because its osmolality and electrolyte composition are similar to those of plasma. Utilizing Ringer's lactate should minimize movement of fluid and electrolytes into or out of the peritoneal cavity. The rather large volume of 2 L was chosen to ensure adequate distribution of drug within the peritoneal cavity (15). A prerinse of 2 L of Ringer's lactate was given to remove protein from the peritoneal cavity and to ensure adequate catheter function. The postrinse was given to aid in the removal of remaining low concentrations of cisplatin. A short dwell time (15–20 mins) was chosen to allow higher concentrations of cisplatin to be administered and yet limit systemic absorption. Since 10–12 mins are required to infuse the drug, at least part of the peritoneum is exposed to the drug for 27–30 mins. Weekly irrigation of the Tenckhoff catheter was thought necessary to ensure patency (10). To minimize the number of times that the catheter was used and hence minimize the chance of infection, we chose to treat on a weekly basis. A trial length of 3 months was determined with the knowledge that with systemic cisplatin, almost all responses will be evident within the first 3 months of chemotherapy (3–5).

Atomic absorption spectroscopy, radioactive tracers, and high-performance liquid chromatography can be used to measure cisplatin. The increased sensitivity of the radioactive tracer assay (detection limit at 2σ level was 0.01 μg/ml) is its major advantage over atomic absorption spectrometry (detection limit at 2σ level of 0.04 μg/ml) (16). The tracer assay is similar to atomic absorption spectrometry in that both measure platinum rather than cisplatin, neither assay being able to distinguish cisplatin from its metabolites. The addition of high-performance liquid chromatography prior to atomic absorption spectrometry enabled Himmelstein et al (17) to compare plasma filterable platinum to plasma filterable cisplatin. During 2 hrs following iv administration, they found a constant ratio of 0.8 and concluded that filterable platinum levels provided a good indication of cisplatin levels, although the actual value was slightly overestimated. Determination of the filterable plasma cisplatin is necessary, as it is that fraction which has activity, the protein-bound drug being inactive (18).

The therapeutic advantage of ip chemotherapy results from increased exposure of the peritoneal tumor without increased exposure of the systemic circulation. The magnitude of the advantage, as shown by Dedrick et al (19), depends on the absorption of the drug from the peritoneal cavity and on its systemic clearance. Decreasing peritoneal absorption and increasing systemic clearance would improve the efficiency of ip chemotherapy. In this study, cisplatin was rapidly absorbed from the peritoneal cavity (only 75% recovered with a dwell time of 20 mins), and was rapidly cleared from the systemic circulation (renal clearance of 94–133 ml/min). This resulted in a cisplatin concentration 42–72 times higher within the peritoneal cavity than within the systemic circulation. This increased exposure of the tumor to cisplatin resulted in three responses in four patients who had previously failed systemic cisplatin.

Although the ratio of the concentration of cisplatin in peritoneal cavity to plasma is instructive, it is not an ideal parameter to study. The area under the concentration versus time curve (AUC) would be a more accurate measure of exposure of peritoneum and systemic circulation to drug. Due to the short dwell times employed, serial measurements of the concentration of cisplatin within the peritoneal cavity were not accomplished. As a result, neither the AUC for the peritoneal cavity nor the ratio of AUC for the peritoneal cavity to AUC for plasma can be deduced from this study. In a similar study utilizing ip cisplatin with a 4-hr dwell time, Howell et al (20) found the mean AUC (peritoneum)/AUC (plasma) to be 12.4. In the study by Howell et al, the dose of cisplatin ranged from 90 to 270 mg/m^2, courses were given every 3 weeks, and sodium thiosulfate, a neutralizing agent which prevents both the toxicity and antitumor effect of cisplatin, was infused iv during ip cisplatin administration. Utilizing this regimen produced a 42% response rate in 12 evaluable patients with peritoneal carcinomatosis.

The importance of schedule, dwell time, and sodium thiosulfate infusion in the effectiveness of ip chemotherapy is unclear. Since iv cisplatin has not been shown to be schedule-dependent (7,21), one might question whether the weekly schedule employed in this study is any more effective than the conventional every-3-week schedule. The peritoneal exposure during ip chemotherapy is ten to 300 times higher than the systemic exposure (20,22,23) and will greatly exceed that required to kill even moderately sensitive tumor cells. It is probable that the high levels of drug found within the peritoneal cavity will penetrate only the most superficial layer of the tumor

TABLE 2.—Clinical history of patients receiving ip cisplatin for residual ovarian carcinoma

Patient No.	Age (yrs)	Date of diagnosis, procedure,* stage, pathology	PAC† chemotherapy (No. of courses)	Disease recurrence or persistence	Tenckhoff placement	Response	Dose of ip cisplatin (mg)	Complications	Subsequent course
1	35	5/80; TAH/BSO, omentectomy; stage III, grade 2; serous adenocarcinoma	9	4/81: 4 × 4 × 5-cm pelvic mass secondarily debulked with sigmoid resection, transverse loop colostomy; confluent disease on diaphragms, studding throughout peritoneal cavity	4/81: open laparoscopy	9/81: confluent disease on diaphragm → 1 × 2-mm disease on diaphragm	120–180	Platelet count decreased to 40,000 cells/mm^3, twice	11/81: *C. parvum* × 2; 1/82: whole-abdominal radiation therapy; ‡ 6/83: no evidence of disease
2	65	6/81; TAH/BSO, omentectomy; stage III, grade 2–3; serous adenocarcinoma	8	3/82: 2-mm disease diffuse on peritoneal surfaces at second-look	3/18/82: open laparoscopy; 4/1/82; minilaparotomy	6/82: laparotomy, no peritoneal studding, but pelvic adhesion positive for adenocarcinoma	120–180	Catheter malfunction requiring new catheter; decrease in creatinine clearance to 40 ml/min on Course 12	7/82: whole-abdominal radiation therapy; ‡ 6/83: no evidence of disease
3	33	3/80; subtotal hysterectomy, BSO, omentectomy; stage IV, grade 3; serous adenocarcinoma	9	12/80: negative at second-look; 8/28/81: laparotomy 1–2-mm nodules on rectum, diaphragm, positive retroperitoneal nodes	8/81: secondary debulking	11/81: negative at laparoscopy; cytology negative × 10	120–270	Abdominal pain with cisplatin dose > 210 mg	12/81: whole-abdominal radiation therapy, ‡ 6/83: no evidence of disease
4	63	6/81; subtotal hysterectomy, BSO, omentectomy; stage III, grade 3; serous adenocarcinoma with sarcomatoid elements	10	3/82: 7–8-mm disease at second-look, nodes negative	3/82: second-look laparotomy	6/82: laparotomy, disease progression from 7–8 mm → 10–15 mm	120–180	None	7/82: abdominal radiation therapy, ‡ progression; 11/82: died

*TAH/BSO = total abdominal hysterectomy/bilateral salpingo-oophorectomy.
†PAC = cisplatin (50 mg/m^2), doxorubicin (50 mg/m^2), and cyclophosphamide (500 mg/m^2) given iv every 3 wks.
‡3000 rads to whole abdomen with renal shield; 4500 rads to pelvis.

(24) and will result in death of only those superficial cells. If the necrotic tumor cells are removed prior to the next drug administration, it may be more efficient to use a dose low enough to be given frequently but still high enough to kill the superficial tumor layer. The question of the most efficient schedule awaits further understanding of the formation of drug gradients within the tumor and the kinetics of necrotic cell removal. Ultimately, the question of schedule will be answered only by prospective trials. Whether the short dwell time (15–20 mins) employed in this study is important in producing response is difficult to discern. As noted before, the therapeutic advantage of ip chemotherapy depends on the high ratio of peritoneal to systemic drug exposure. The peritoneal AUC divided by the absorbed dose (A) is one measure of this therapeutic advantage. If first-order kinetics and nonsaturable transport are assumed, it can be shown that the ratio of peritoneal AUC to A is inversely proportional to the product of the drug permeability and the effective peritoneal surface area (*see* Appendix). Since the ratio of peritoneal Auc to A is not a function of dwell time, we would not expect a short dwell time to significantly affect the therapeutic advantage of ip chemotherapy. This conclusion may be open to criticism in that the above calculations treat the peritoneum as a simple membrane and ignore the period of disequilibrium at the very beginning of the peritoneal infusion. Utilizing a neutralizing substance such as a sodium thiosulfate systemically while using cisplatin ip is intriguing, but the possibility of the sodium thiosulfate protecting not only the kidney but the tumor as well must be considered.

The response to ip cisplatin in three patients who have previously failed iv cisplatin is noteworthy. It implies that the effectiveness of cisplatin against peritoneal carcinomatosis could be improved if the ip rather than the iv route were employed. Studies in a dog model have shown levels of cisplatin in tissues outside the peritoneal cavity to be equal for both iv and ip cisplatin (9). Hence, the ip route might be used to treat systemically as well. Ip cisplatin administered in conjunction with other systemic or ip drugs is a possibility for future consideration. Prior to such a study, a larger experience with the ip route of administration will be required. To optimize the schedule of ip chemotherapy, knowledge of the basic transport phenomenon within the peritoneal cavity is necessary. The present phase I study is continuing in order to gain more experience, and a murine ovarian tumor model is being utilized to study basic peritoneal transport physiology.

APPENDIX

If the amount of drug in the peritoneal cavity (A), time (t), permeability of peritoneal membrane (ρ), effective surface area of the peritoneum (S), volume of peritoneal dialysate (V), drug concentration within the peritoneal cavity (C), and drug concentration within the plasma (C_p) are defined, then:

$$\frac{dA}{dt} = -\rho S \left(\frac{A}{V} - C_p\right) \qquad [1]$$

If $\frac{A}{V} \gg C_p$, and V, ρ, and S are not functions of time, equation [1] can be solved for A where A_o is the initial amount of drug administered.

$$A = A_o e^{-\frac{\rho S}{V} t} \qquad [2]$$

The ratio of the area under the concentration versus time curve for peritoneal exposure (Auc) to absorbed dose (A^*) can then be deduced:

$$\frac{Auc}{A^*} = \frac{\int_0^t C\,dt}{A_o - A} = \frac{\frac{C_o V}{\rho S}\left(1 - e^{-\frac{\rho S}{V} t}\right)}{C_o V \left(1 - e^{-\frac{\rho S}{V} t}\right)} = \frac{1}{\rho S} \qquad [3]$$

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Anticipatory Nausea and Vomiting in an Ambulatory Medical Oncology Population[1,2]

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We studied the prevalence of anticipatory nausea (AN) and anticipatory nausea and vomiting (ANV) in an ambulatory medical oncology population by self-report questionnaire over 7 weeks. Thirty-eight of 123 (31%) patients receiving parenteral chemotherapy reported anticipatory symptoms (AN or ANV). Twenty-one (17%) patients reported ANV and 17 (14%) reported AN only. Patients receiving parenteral chemotherapy (N = 123) with anticipatory symptoms (N = 38) were younger (45.1 ± SE 1.9 vs 55.5 ± 1.45, $P < 0.001$) and more likely to be female (82% vs 61%, $P = 0.04$), unmarried (47% vs 26%, $P = 0.03$), and receiving adjuvant chemotherapy for breast cancer (42% vs 7% $P < 0.001$) than patients without anticipatory symptoms (N = 85). A greater proportion of patients with both postchemotherapy nausea and vomiting and anticipatory symptoms reported > 12 hours of postchemotherapy nausea (65% vs 39%, $P = 0.01$) and postchemotherapy nausea and vomiting (37% vs 12%, $P = 0.01$) after their most recent cycle of chemotherapy than did patients with postchemotherapy symptoms only. In structured interviews with 23 patients with anticipatory symptoms, 16 identified specific stimuli associated with AN or ANV, taste being the most frequently mentioned (ten of 16 patients) sensory modality. In our clinic, patients receiving adjuvant chemotherapy for breast cancer develop anticipatory symptoms frequently and represent a relatively homogenous sample for further studies. [Cancer Treat Rep 67:1093–1098, 1983]

Anticipatory nausea and vomiting (ANV) occurs prior to or during the administration of regularly scheduled parenteral chemotherapy in patients with previous postchemotherapy nausea and vomiting (PCNV). Anticipatory symptoms appear after four or five cycles of chemotherapy (1). The development of anticipatory symptoms has been described in terms of a respondent conditioning paradigm, but their pathogenesis is unknown (2). Anticipatory symptoms have been associated with the following: younger age, cisplatin, and severe, prolonged PCNV (3); taste sensations during chemotherapy injections, and anxiety (4–6); stage of disease (7); emotional distress and poor coping (8); and neuroticism and elevations in state and trait anxiety (9). ANV responds poorly to antiemetics as currently prescribed but is responsive to muscle relaxation and hypnotherapies (10–13).

The prevalence of anticipatory symptoms varies from 21% to 65%, depending on the characteristics of the sample (3,4,6,9).[6] We found that 33% of women participating in a comparison of standard and low-dose cyclophosphamide, methotrexate, and 5-FU (CMF) for adjuvant treatment of breast cancer developed ANV (14). This was somewhat surprising, since we had not considered CMF severely emetogenic. To replicate this finding and estimate the frequency of anticipatory symptoms in other treatment groups, we determined the prevalence of anticipatory nausea (AN) and ANV in our medical oncology clinic. Additionally, we determined associations with demographic, diagnostic, and treatment variables.

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METHODS

During the 7-week period from June 1 to July 24, 1981, we surveyed the medical oncology clinic of The Johns Hopkins Oncology Center by self-report questionnaire to ascertain the prevalence of anticipatory symptoms. A 7-week survey was chosen because 6 weeks is the longest commonly encountered treatment cycle of our clinic; an additional week was added to include patients who had their treatment delayed for any reason. Patients were eligible if they had malignancies treated in our outpatient clinic and a return visit by nurse or physician during the 7-week period. Patients attending clinic more than once during this period had their first response to the questionnaire counted. None of the patients surveyed participated in our earlier study (14).

The self-report questionnaire contained 14 yes/no or multiple choice questions concerning the presence of nausea and/or vomiting before, during, and after chemotherapy. Patients were asked about the duration of postchemotherapy nausea (PCN) and PCNV after their previous cycle of chemotherapy, but no attempt was made to define the severity of postchemotherapy symptoms. The questionnaire was given to the patient by a member of the clinic's administrative staff, completed while waiting to be seen by physician or nurse, and returned to the administrative staff member.

Our definitions of AN and ANV were nausea or nausea and vomiting before or during the administration of chemotherapy without another cause for nausea and/or vomiting. To estimate false-positive (ie, patients whose questionnaire responses suggested anticipatory symptoms but who, in fact, did not have AN or ANV) and false-negative (ie, patients whose questionnaire responses did not suggest anticipatory symptoms but who, in fact, had AN or ANV) rates with our questionnaire, a separate sample of 88 medical oncology patients was asked to complete the questionnaire. Each patient was then interviewed by an investigator (V. R. Sheidler) who was unaware of the patient's responses on the questionnaire. The interviewer asked questions about nausea and/or vomiting before, during, and after chemotherapy. The interviewer then used standard criteria to determine whether the patient had anticipatory symptoms. By comparing the interviewer's ratings with the patient's self-reports, we estimated both the false-positive and false-negative rates to be 7%.

We obtained the age, sex, marital status, race, diagnosis, and current treatment for all eligible patients. The eligible sample had a variety of diagnoses and received varied treatments. Certain diseases (eg, breast cancer) and treatments (ie, CMF-containing regimens) were common, while other diseases (ie, pancreatic cancer and melanoma) and treatments (eg, cisplatin) were rare. To facilitate the comparison of patients with and without anticipatory symptoms, we developed diagnostic and treatment categories. When diseases or treatments were common, categories were quite homogenous but when diseases or treatments were rare, they were combined into more heterogenous groups (table 1).

To test the representativeness of our surveyed sample, we compared the age, sex, race, marital status, and diagnostic and treatment categories of patients who completed the questionnaire with eligible patients who did not complete the questionnaire. Patients completing the questionnaire were initially divided into "treatment" and "no treatment" groups. The "treatment" group included those patients receiving oral and parenteral treatment. Patients receiving "treatment" were then categorized as having no nausea or vomiting, postchemotherapy nausea and/or vomiting, or anticipatory nausea and/or vomiting.

To better differentiate and characterize patients with and without anticipatory symptoms, we compared the age, sex, race, marital status, and diagnostic and treatment categories of patients receiving parenteral treatment with and without AN or ANV. Patients without anticipatory symptoms included both patients with PCNV only and patients with no nausea and vomiting. Since nausea and vomiting were rare with oral chemotherapy and hormonal treatments, we limited our prevalence calculations and comparisons to only those patients on parenteral chemotherapy. For these comparisons, Chi-square or "t" tests were employed.

Finally, 23 of 40 patients with anticipatory symptoms underwent a follow-up structured interview to better define the ANV syndrome. Failure to interview all 40 patients resulted from cessation of treatment, cognitive dysfunction, death, or unwillingness of the patient.

RESULTS

Sample Characteristics

Of 446 eligible patients, 298 (67%) completed the questionnaire. Table 1 compares the demographic, diagnostic, and treatment characteristics of the total eligible, surveyed, and nonsurveyed eligible samples. Only two differences between the surveyed and nonsurveyed eligible populations tended towards or achieved statistical significance. The proportion of patients with small cell carcinoma of the lung (SCCL) was higher in the nonsurveyed sample (11% vs 6%, $P = 0.08$). Likewise, the proportion of patients receiving hormonal treatment was higher in the nonsurveyed sample (12% vs 6%, $P = 0.03$).

Of the 298 patients surveyed, 136 (46%) were receiving "no treatment," 33 (11%) were receiving oral alkylating agents or hormones, and 129 (43%) were receiving parenteral chemotherapy. Complete nausea and vomiting data were available for 123 of 129 patients receiving parenteral treatment. The prevalence figures subsequently presented are derived from this sample of 123 patients.

TABLE 1.—Demographic, diagnostic and treatment characteristics of eligible, surveyed, and nonsurveyed samples with comparison of surveyed and nonsurveyed samples

Characteristic	No. of patients (%)— Eligible (N = 446)	Surveyed (N = 298)	Nonsurveyed (N = 148)	Significance of difference
Demographics				
Female	289 (65)	190 (64)	99 (67)	NS*
White	344 (77)	230 (77)	114 (77)	NS
Married	280 (63)	191 (64)	89 (60)	NS
(mean age in yrs ± SE)	(53.7 ± 0.67)	(53.5 ± 0.85)	(55.2 ± 1.05)	NS
Diagnosis				
Primary or regional breast	62 (14)	45 (15)	17 (11)	NS
Metastatic breast	100 (22)	64 (21)	36 (24)	NS
Gastrointestinal tract	27 (6)	18 (6)	9 (6)	NS
Small cell carcinoma of the lung	33 (7)	17 (6)	16 (11)	$P = 0.08$
Hodgkin's disease	35 (8)	26 (9)	9 (6)	NS
Non-Hodgkin's lymphoma	64 (14)	37 (12)	27 (18)	NS
Myeloma	39 (9)	28 (9)	11 (7)	NS
Miscellaneous	86 (19)	63 (21)	23 (16)	NS
Treatment				
Adjuvant CMF	30 (7)	24 (8)	6 (4)	NS
Nonadjuvant CMF	25 (6)	19 (6)	6 (4)	NS
Doxorubicin-containing	68 (15)	46 (15)	22 (15)	NS
Iv alkylating agent-containing	28 (6)	19 (6)	9 (6)	NS
Oral alkylating agent-containing	25 (6)	16 (5)	9 (6)	NS
Hormonal	35 (8)	17 (6)	18 (12)	$P = 0.03$
Miscellaneous	32 (7)	21 (7)	11 (7)	NS
No treatment	203 (46)	136 (46)	67 (45)	NS

*NS = not significant.

Prevalence of Anticipatory Symptoms

Twenty-one of 123 (17%) patients reported ANV and an additional 17 (14%) reported AN only, for a total of 38 of 123 (31%) patients with anticipatory symptoms. Two additional patients reported anticipatory symptoms, but were excluded because of difficulties encountered in classifying their treatment. One patient with metastatic breast cancer was receiving megestrol acetate at the time of the survey. She had recently been switched from CMF treatment, which had presumably contributed to her anticipatory symptoms. A second patient with myeloma, who was receiving "no treatment" at the time of the survey, had presumably developed anticipatory symptoms with an earlier doxorubicin and carmustine regimen.

Characteristics of Patients With Anticipatory Symptoms

The 38 patients with anticipatory symptoms had a mean age of 45.1 ± 1.9 years. Thirty-one (82%) patients were female, 20 (53%) were married, and 26 (68%) were white. Sixteen (42%) patients had primary or regional breast cancer, 11 (29%) had metastatic breast cancer, and four (11%) had Hodgkin's disease. No other diagnostic category contained more than two patients. Sixteen (42%) patients with anticipatory symptoms were receiving adjuvant CMF, while five (12%) were given nonadjuvant CMF. Twelve patients (32%) received doxorubicin-containing regimens. No other treatment category contained more than three patients. All 38 patients with anticipatory symptoms reported prior postchemotherapy symptoms and were currently receiving parenteral chemotherapy.

Prevalence of Anticipatory Symptoms in Each Diagnostic and Treatment Group

Tables 2 and 3 show the prevalence of anticipatory symptoms in each diagnostic and treatment group for 123 patients given parenteral treatment. Seventy-three percent of patients with primary or regional breast cancer receiving parenteral chemotherapy reported anticipatory symptoms, compared to 29% of patients with metastatic breast cancer. In patients with Hodgkin's disease who were receiving parenteral chemotherapy, the prev-

alence was 33%. All other diagnostic groups had a prevalence < 20%. Sixteen of 22 (73%) patients given adjuvant CMF reported anticipatory symptoms, compared to 28% of patients given CMF as nonadjuvant treatment. Twenty-six percent of patients receiving doxorubicin-containing regimens reported anticipatory symptoms. Every other treatment regimen had a prevalence < 20%.

Comparison of Patients With and Without Anticipatory Symptoms

Table 4 divides patients given parenteral treatment (N = 123) into those with (N = 38) and without (N = 85) anticipatory symptoms and compares their age, sex, race, and marital status. Also compared are the proportions of patients with primary or regional and metastatic breast cancer and the proportions of patients treated with adjuvant CMF, nonadjuvant CMF, and doxorubicin-containing regimens. Since there were fewer than five patients with anticipatory symptoms in all remaining diagnostic and treatment groups, we did not attempt a statistical comparison in those groups.

Patients with anticipatory symptoms were significantly younger (45.1 ± 1.9 vs 55.5 ± 1.45, $P < 0.001$), more likely to be female (82% vs 61%, $P = 0.04$), and less likely to be married (53% married vs 74%, $P = 0.03$) than the group without anticipatory symptoms. Sixteen patients (42%) with anticipatory symptoms had primary or regional breast cancer and were being treated with adjuvant CMF, compared to six (7%) in the group without such symptoms ($P < 0.001$). There were no other differences between the two groups.

Relationship Between Anticipatory Symptoms and Duration of Postchemotherapy Nausea and/or Vomiting After Previous Cycle of Parenteral Chemotherapy

To analyze the relationship between anticipatory and postchemotherapy symptoms, we compared the reported duration of postchemotherapy nausea and/or vomiting after the previous cycle of chemotherapy in patients with anticipatory and postchemotherapy symptoms only. We removed the group without any nausea and vomiting from this comparison.

Twenty-six of 38 (68%) patients with anticipatory symptoms reported PCN lasting ≥ 12 hours, compared to 19 of 49 (39%) in the group with postchemotherapy symptoms only ($P = 0.011$). Fourteen of 38 (37%) patients with anticipatory symptoms reported postchemotherapy vomiting lasting ≥ 12 hours, compared to six of 49 (12%) in the group with postchemotherapy symptoms only ($P = 0.014$).

Interview Results

In structured interviews, 16 of 23 (70%) patients reported the onset of symptoms the morning of scheduled treatment, while six (26%) reported symptoms the day before. Twelve (52%) patients stated that symptoms occurred while they were at home or in places other than the clinic, while seven (30%) reported that symptoms were limited to the clinic.

Sixteen (70%) patients identified specific sensory stimuli associated with AN or ANV, and all but one of the 16 reported multiple stimulus associations. Ten (43%) patients identified distinctive tastes, nine (39%) reported visual events, three (13%) reported sounds, and six (26%) reported tactile stimuli. Five (22%) patients stated that merely waiting in the clinic precipitated symptoms.

TABLE 2.—Prevalence of anticipatory symptoms by diagnosis for patients receiving parenteral chemotherapy

Diagnosis	No. of patients with anticipatory symptoms (%)
Primary or regional breast (N = 22)	16 (73)
Metastatic breast (N = 38)	11 (29)
Gastrointestinal tract (N = 8)	1 (13)
SCCL (N = 11)	2 (18)
Hodgkin's disease (N = 12)	4 (33)
Non-Hodgkin's lymphoma (N = 14)	2 (14)
Myeloma (N = 4)	0 (0)
Miscellaneous (N = 11)	2 (18)

DISCUSSION

The 31% prevalence for anticipatory symptoms in patients on parenteral chemotherapy is consistent with that reported by some investigators (3,4,6,9), but differs significantly from the 65% figure in patients receiving cisplatin for gynecologic and genitourinary neoplasms.[6] This difference is partially explained by the small number of patients treated with cisplatin in our clinic. Since the prevalence rates were computed for patients given parenteral chemotherapy, the significant under-representation of patients in our surveyed group receiving hormonal therapy would not affect the prevalence rates.

TABLE 3.—Prevalence of anticipatory symptoms by treatment regimen for patients receiving parenteral chemotherapy

Treatment regimen	No. of patients with anticipatory symptoms (%)
Adjuvant CMF (N = 22)	16 (73)
Nonadjuvant CMF (N = 18)	5 (28)
Doxorubicin-containing (N = 46)	12 (26)
Iv alkylating agent-containing (N = 17)	2 (12)
Miscellaneous (N = 16)	3 (19)

Likewise, the trend towards under-representation of patients with SCCL in the surveyed group probably did not significantly affect prevalence rates or associations with anticipatory symptoms. The proportion of patients with SCCL receiving active treatment was higher in the surveyed than in the nonsurveyed group, and the treatment regimens in both groups were similar. Prevalence rates are affected not only by the diagnostic and treatment characteristics of the sample, but also by the methods employed for determining prevalence (1). Morrow (3) evaluated patients about to receive their fourth cycle of chemotherapy and found a prevalence of 21% for ANV, which is quite similar to our figure of 17% obtained without regard to treatment cycle. The accuracy of our prevalence figures is slightly limited by the 7% false-positive and false-negative case rates associated with the questionnaire.

CMF-containing regimens were associated with anticipatory symptoms when given as adjuvant therapy, but not when given for metastatic disease. To better understand this difference, we compared the treatment regimens in the two groups. We were unable to compare the adjuvant CMF-treated patients to the other treatment groups (eg, doxorubicin-containing, etc), because of the heterogeneity of the latter. The average doses of CMF per meter squared were comparable in the two groups. The fraction of patients on prednisone-containing regimens was also comparable. However, the median cycle number for the 22 patients receiving CMF as adjuvant therapy was seven, compared to three for patients receiving CMF for metastatic disease. Furthermore, the proportion of patients receiving adjuvant CMF with PCN lasting ≥ 12 hours after their most recent cycle of chemotherapy was 13 of 22 (59.1%), compared to five of 18 (27.8%) for patients receiving CMF for metastatic disease ($P = 0.03$). The proportion of patients receiving adjuvant CMF with postchemotherapy vomiting lasting ≥ 12 hours was also greater than the fraction given CMF for metastatic disease, but not significantly so (five of 22 [22.7%] vs two of 18 [11.1%], P = NS). Therefore, patients receiving adjuvant CMF may have been at greater risk to develop anticipatory symptoms, because they had received more cycles of treatment which produced more prolonged PCNV. This finding would be consistent with a respondent conditioning paradigm (2). We do not know why patients receiving adjuvant CMF might have had more prolonged PCNV than patients given CMF for metastatic disease. It is possible that there were differences in the antiemetic regimens prescribed for the two groups. There have been reports of differential toxic effects experienced by women who received adjuvant chemotherapy, as compared to women who received chemotherapy for metastatic disease (15). The emotional and cognitive responses of women receiving adjuvant CMF are different than those of women receiving CMF for metastatic disease. Such differences in emotional and cognitive responses may contribute to differential rates of nausea and vomiting.

Since patients receiving adjuvant CMF are generally younger women, it is possible that the adjuvant patients accounted for the association between age, sex, and anticipatory symptoms. Morrow (3) reported that patients with ANV were significantly younger, without noting an association with sex or adjuvant CMF for breast cancer. When the 16 patients with adjuvant CMF are removed from the group with anticipatory symptoms, the mean age of the remaining 22 patients is 45.5 years, which is still significantly younger than patients without symptoms. This suggests that younger patients in general may be more likely to develop this syndrome. Whether this is

TABLE 4.—Demographic, diagnostic and treatment regimen comparisons of patients given parenteral chemotherapy with and without anticipatory symptoms

	No. of patients (%)—		
	With anticipatory symptoms (N = 38)	Without anticipatory symptoms (N = 85)	Significance of difference
Demographic			
Female	31 (82)	52 (61)	$P = 0.04$
Married	20 (53)	63 (74)	$P = 0.03$
Caucasian	26 (68)	67 (79)	NS*
(mean age in yrs ± SE)	(45.1 ± 1.9)	(55.5 ± 1.45)	$P < 0.001$
Diagnosis			
Primary or regional breast	16 (42)	6 (7)	$P < 0.001$
Metastatic breast	11 (29)	27 (32)	NS
Treatment regimen			
Adjuvant CMF	16 (42)	6 (7)	$P < 0.001$
Nonadjuvant CMF	5 (12)	13 (15)	NS
Doxorubicin-containing	12 (32)	34 (40)	NS

*NS = not significant.

a function of age alone or some age-related treatment differences remains to be determined. The association between the female sex and anticipatory symptoms is probably accounted for by the association with adjuvant CMF. When the 16 adjuvant CMF patients are removed from the sample with anticipatory symptoms, the significant sex difference between the groups disappears.

It is difficult to explain the association between anticipatory symptoms and being unmarried. The unmarried group was heterogenous, being comprised of patients who were single, separated, divorced, and widowed. Marital status was not associated with anticipatory symptoms in Morrow's study (3). It is possible that support from a spouse in some way ameliorated chemotherapy-associated vomiting. This finding will require repetition in future studies.

We did not collect data on the education or socioeconomic status of our patients. Some have speculated that highly educated, intellectually oriented patients are more susceptible to anticipatory symptoms. This interesting hypothesis deserves testing in future studies.

The PCNV data in this survey were limited to the presence and duration of postchemotherapy symptoms after the previous cycle of chemotherapy. It does not represent a detailed history of postchemotherapy symptoms. Nevertheless, the finding that patients with anticipatory symptoms are more likely to have had previous, prolonged postchemotherapy symptoms is consistent with the respondent conditioning paradigm proposed to describe the phenomenon and Morrow's findings (2,3). Once a patient develops anticipatory symptoms, his postchemotherapy symptoms may worsen, accounting for, in part, the association between anticipatory symptoms and severe, prolonged postchemotherapy symptoms. On the other hand, Morrow (3) found a strong association between postchemotherapy and anticipatory symptoms early in the development of anticipatory symptoms (at the fourth cycle of chemotherapy), suggesting that severe and prolonged PCNV precede the development of anticipatory symptoms and are not simply the product of such symptoms.

Since we interviewed only 23 of 40 patients with anticipatory symptoms, the results may not be entirely representative. However, our findings are consistent with previous reports. It has been noted that symptoms are the most intense in the clinic prior to treatment, but can occur at other times and in other locations (1). Taste was the most commonly reported sensory modality associated with anticipatory symptoms, and it is the only sensory modality that has been found to be significantly associated with anticipatory symptoms (4-6).

These findings support our previous report and reveal that women treated with adjuvant CMF are the largest relatively homogenous group with anticipatory symptoms in our clinic (14). Further studies on the pathogenesis of anticipatory symptoms in this clinic will be performed with this population.

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Heart Size and Function After Radiation Therapy to the Mediastinum in Patients With Hodgkin's Disease[1,2]

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Changes in the transverse heart diameter and cardiothoracic ratio were determined by comparing the pretreatment and last follow-up posteroanterior chest x-rays of 96 patients with stage I–III Hodgkin's disease who had received radiation therapy (RT) to the mediastinum, with the same parameters observed in 20 similar patients whose mediastinum was not irradiated. A significantly higher proportion of patients who had received RT to the mediastinum had a decrease in transverse heart diameter and cardiothoracic ratio. Among patients presenting with a large mediastinal mass, these changes were more pronounced as compared to the other groups; however, this difference was not of statistical significance. First-pass left ventricular ejection fraction (LVEF) performed with ^{99m}Tc pertechnetate (obtained in 55 of these patients 30–120 months after RT to the mediastinum) was compared with the LVEF of 20 normal controls. The control group had a significantly higher LVEF than the group of patients who had received RT to the mediastinum. No correlation was observed between changes in these parameters and the use of adjuvant, salvage, or no chemotherapy after mediastinal RT. None of these patients presented congestive heart failure or constrictive pericarditis, but our findings indicate a subclinical cardiomyopathy in more than one-half of the patients who received RT to the mediastinum, suggesting that the incidence of heart damage after mediastinal RT might be higher than expected. Prospective studies are necessary to elucidate the incidence and implications of this potentially serious complication. [Cancer Treat Rep 67:1099–1103, 1983]

Radiation therapy (RT) to the mediastinum given for the treatment of Hodgkin's disease (HD) was reported to be well-tolerated and produced only temporary damage to the heart and other mediastinal structures. However, severe damage to the pericardium (1), acute myocardial infarction (2,3), valvular disease (4), cardiomyopathy (5,6), and arrhythmia (7) have been reported in these patients.

We previously reported the abnormalities in heart size and function detected by x-ray and radionuclide studies in patients with HD who had received RT to the mediastinum (8). A more extensive and comprehensive study of such abnormalities is presented here.

MATERIALS AND METHODS

The pretreatment and the last follow-up posteroanterior (PA) chest x-rays of 97 of 120 patients with stage I–III HD who had received initial RT to the mediastinum at this institution between April 1971 and May 1979 were retrospectively reviewed. These patients were part of a prospective randomized study of treatment of early stages of HD. Sections of that study were published elsewhere (8–10). The transverse heart diameter (THD) and the cardiothoracic (C:T) ratio were measured according to standard techniques by one radiologist (J. Park), who was not aware of the treatments

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given to these patients. At admission, these patients ranged in age from 15 to 56 years; the median age was 24 years. None of these patients had symptoms or clinical findings of heart disease or hypertension. Thirty-five patients (Group 1) had a large mediastinal mass and/or left hilar adenopathy, 26 (Group 2) had a smaller mediastinal mass, and 36 (Group 3) had no mediastinal mass. We defined large mediastinal mass as that occurring when the ratio between the maximum width of the mediastinal tumor divided by the maximum intrathoracic ratio was > 0.33. The THD and the C:T ratio of these 97 patients were compared to similar parameters of 20 other patients with stage I-II HD (part of the same prospective study, Group 4), without heart disease or hypertension, and treated without RT to the mediastinum. The control group ranged in age from 17 to 62 years (median, 32), and the follow-up ranged from 36 to 120 months (median, 91). RT to the mediastinum was delivered through anterior and posterior fields each day to a *constant* mid-tumor dose of 3600 rads. When delivered to a large treatment field, the daily dose was 150 rads. When smaller fields were used (ie, mediastinum alone) the daily dose was 200 rads. The total number of days over which thoracic RT was delivered ranged from 25 to 35 days (median, 35). Megavoltage radiation was used in all cases. RT for all patients was planned before treatment, using a simulator. The mid-cardiac doses ranged from 3240 to 3600 rads (median, 3500; mean, 3484). Involved-field (IF) RT was given to 21 patients in Group 1, to 16 in Group 2, and to 12 in Group 3. Total-nodal irradiation (TNR) was given to 14 patients in Group 1, to ten in Group 2, and to 24 in Group 3. Treatment in these patients is summarized in table 1. Patients in Group I received RT to 75%-100% of the heart. Those patients without mediastinal and/or left hilar masses (Group 3) received the least RT to the heart, since most of the heart (≥ 50%) was not exposed. For patients in Group 2, the amount of heart irradiation was intermediate between that of Group 1 and Group 3. Scatter radiation to the cardiac area from lower torso irradiation was found to be minimal. The follow-up in these patients from first to last chest x-ray ranged from 36 to 128 months; the median follow-up was 86 months.

Six cycles of adjuvant chemotherapy were given 4 weeks after completion of RT to 38 patients (20 after IF RT and 18 after TNR). Fifteen patients in the control group received adjuvant chemotherapy in addition to RT. The chemotherapy program used in this study has been reported previously (9). It consisted of monthly combinations of vincristine and procarbazine alternating with vinblastine, chlorambucil, and prednisone. Nineteen patients who relapsed after RT (six after IF RT and 13 after TNR) received salvage chemotherapy with mechlorethamine, vincristine, procarbazine, and prednisone (11) or with similar programs of combination chemotherapy (12). Those patients who received doxorubicin-containing regimens and/or those who had the mediastinum re-treated with RT were excluded from this study. Chemotherapy is summarized in table 1.

First-pass left ventricular ejection fraction (LVEF) was performed using the System 77 scintiscanner in the left anterior oblique (45°) position with ^{99m}Tc pertechnetate in 55 of these patients 30-120 months after RT to the mediastinum (median, 82 months). The age of these patients ranged from 21 to 60 years (median, 32). The prechemotherapy LVEF of 18 consecutive patients with various cancers and without clinical, electrocardiographic, or radiologic evidence of heart disease and who had not received previous RT to mediastinum were used as controls. These patients ranged in age from 14 to 80 years (median, 60).

Statistical differences between groups were calculated with the one-way analysis of variance (13).

RESULTS

Heart Size and C:T Ratio

The differences observed in THD and C:T ratio between the pretreatment and last follow-up chest x-rays in the four different groups are shown in figures 1 and

TABLE 1.—Summary of treatments given to 97 patients who received mediastinal RT*

	Group		
	1 (large mediastinal mass)	2 (small mediastinal mass)	3 (no mediastinal mass)
IF RT	21	16	12
TNR	14	10	24
Total	35	26	36
Adjuvant chemotherapy	14	11	13
Salvage chemotherapy	7	5	7

*Values = No. of patients. *See* text for definition of large and small mediastinal mass.

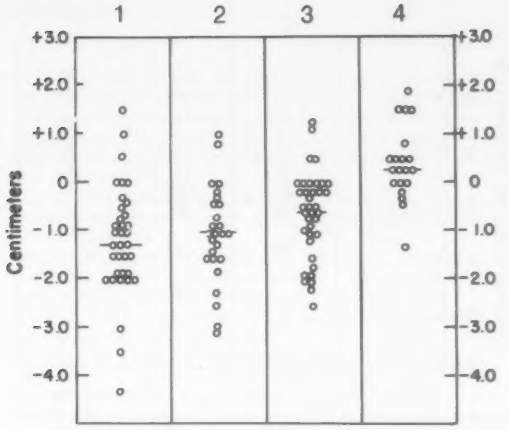

FIGURE 1.—Change observed comparing pretreatment heart size with that determined from the most recent posttreatment PA chest film is expressed in centimeters. Horizontal bars indicate median values for each group. The 3 groups of patients who received mediastinal RT (Groups 1, 2, and 3, *see* text) showed a significant decrease in heart size compared to the patients who did not receive mediastinal RT (Group 4).

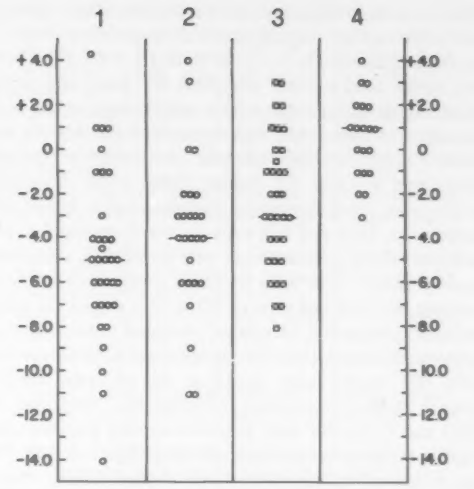

FIGURE 2.—Comparison of pretreatment C:T ratio with that determined from the most recent posttreatment PA chest film. Horizontal bars indicate median value for each group. The 3 groups of patients who received mediastinal RT (Groups 1, 2, and 3, *see* text) showed a significant decrease in heart size compared to the patients who did not receive mediastinal RT (Group 4).

2, respectively. Changes of greater magnitude were observed after RT to the mediastinum, and consisted of a trend in decrease in THD and C:T ratio. These changes were significantly different among the four groups by the one-way analysis of variance ($P < 0.01$), with Group 4 being significantly different from the other three groups ($P < 0.05$).

Two patients included in Group 1 have died. One patient died of HD at 62 months. She had a decrease in heart size of 2 cm at x-ray examination, and at autopsy, her heart was atrophic (175 g), presenting multiple areas of severe fibrosis in the ventricular walls and some in the pericardium. The other patient died with HD in complete response, from acute nonlymphocytic leukemia (ANLL) at 95 months. On x-ray, his heart showed a decrease in size of 1 cm before the onset of the ANLL. On autopsy, his heart weighed 300 g and there was minimal fibrosis in the pericardium. Both patients had severe atherosclerotic changes.

Left Ventricular Ejection Fraction

Figure 3 shows the LVEF of 55 patients who had received RT to the mediastinum, distributed according to the size of the mediastinal mass and of 18 controls (Group 4). The LVEF was significantly different among the four groups ($P < 0.0001$), with Group 4 being significantly different from the other three ($P < 0.01$). Twelve and 16 patients who received RT to the mediastinum presented a frankly abnormal LVEF (< 43%) and a borderline low LVEF (< 50%), respectively. Patients with large mediastinal mass (Group 1) had a higher proportion of abnormal or borderline abnormal LVEF compared to groups with small or no mediastinal mass (Groups 2 and 4); however, this difference was not of statistical significance (fig 3). All of the abnormalities in LVEF observed were of global hypokinesia. Although patients with frankly abnormal LVEF also presented a marked decrease in heart size, abnormal LVEF was observed in patients without or with little change in heart size.

Chemotherapy

The role of chemotherapy (adjuvant or salvage) was investigated among those patients who had received RT to the mediastinum. There were no differences in the proportion of magnitude of change in heart size, C:T ratio, or LVEF according to whether or not the patient received adjuvant chemotherapy, salvage chemotherapy, or no chemotherapy.

DISCUSSION

Pierce et al (14) reported a transient decrease in the THD of most patients undergoing RT to the mediastinum or other large areas, with return to normal after a few months. However, nearly 20% of the patients presented chronic pericardial effusion which resulted in enlargement of the heart shadow in chest x-rays. More recently, Applefeld et al (15) reported con-

strictive pericarditis, occlusive coronary artery disease, and other cardiac hemodynamic abnormalities (detected by fluid challenge) in 24 of 25 patients with HD. These two series used anterior-weighted RT ports and somewhat higher RT dosage, which might explain the high incidence of pericardial and myocardial damage. In the present study, we used anterior and posterior opposed fields and a lower RT dosage (3600 rads). However, 3–10 years after treatment, we observed a significant decrease in THD and C:T ratio in nearly one-half of the patients whose mediastinum was irradiated, compared to only minor variations in these parameters in those patients who did not receive RT to this region. In some patients pericardial effusions produced either by the large mediastinal mass or by pericardial involvement with HD might have produced an apparent cardiomegaly before treatment; nevertheless, decreases in THD and C:T ratio were observed among patients presenting small or no mediastinal mass (figs 1 and 2). We are aware of the relatively poor reproducibility measuring the THD. However, the statistically significant lower magnitude of changes in heart size observed in the control group (same disease, similar age and follow-up) validate our observations.

In about one-half of the patients tested, the first-pass LVEF obtained by radionuclide studies was abnormal or borderline abnormal. Since these studies were obtained retrospectively we do not have pretreatment LVEF for comparison. Nevertheless, lower LVEF values (fig 3) as well as the proportion of abnormal ones were significantly higher in patients whose mediastinum received RT as compared to those observed in the "normal" control group, despite the fact that the controls were markedly older (median age at the time of LVEF study for patients with RT to mediastinum, 32 years; median age control group, 60 years).

The decrease in heart size and the global abnormalities observed in LVEF suggest that RT to the mediastinum produced a diffuse subclinical myocardiopathy. None of the patients tested had findings suggestive of constrictive pericarditis, but one of the two patients who died in this study at autopsy had severe fibrosis in the myocardium and some fibrosis in the pericardium. Echocardiogram studies performed in the few patients presenting radiologic evidence of decreased THD showed that the ventricular walls were frankly subnormal or in the low normal range. However, there were very few studies from which to derive conclusions and, on the other hand, the absence of pretreatment echocardiographic measurements decreases the value of these observations. Gottdiener et al (16) recently reported a significantly lower systolic left ventricular function and decreased left ventricular reserve determined by radionuclide angiocardiography in patients with HD whose mediastinum was irradiated, as compared to normal controls. These investigators also found a decrease in the size of the left ventricular cavity (detected by echocardiography) in the same population of patients.

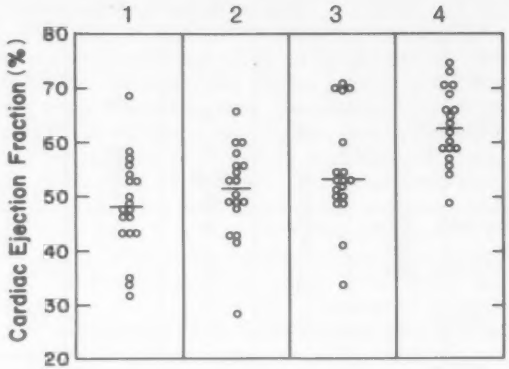

FIGURE 3.—First-pass LVEF obtained before treatment in Group 4 and after mediastinal RT in Groups 1, 2, and 3. Horizontal bars indicate median values for each group. The 3 groups of patients who received mediastinal RT had significantly lower LVEF compared to the patients in Group 4, who did not receive mediastinal RT (Group 4).

Boivin and Hutchinson (17) found a higher cumulative probability of death from heart disease among patients with HD whose heart was irradiated, although not at a significant level. On the other hand, the implications of heart damage in these patients should not be considered only in death rate. Most patients in the present series are young and probably cured of HD and are therefore candidates for long survival. The abnormalities described here might be potential factors for early limitation of activity and/or productivity as well as for a high incidence of clinical heart disease (coronary or other) at a later time. In case of disseminated relapse with HD, a number of patients from this study might not be candidates to receive effective salvage treatments with drugs which produce substantial cardiotoxicity (18).

RT to the mediastinum with conventional dose and techniques as given in this study resulted in subnormal or frankly abnormal heart function in more than one-half of the patients. This proportion is much higher than previously suspected. Longer follow-up is necessary to determine if the abnormalities disclosed by the radionuclide techniques are specific and sensitive indicators of heart disease (19). Prospective studies of cardiac function with noninvasive techniques before and after treatment in patients undergoing mediastinal radiation are necessary to provide important information about the true incidence and the natural course of this potentially serious complication.

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Nephrotoxicity of Semustine[1]

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Semustine is an investigational cancer chemotherapeutic agent in widespread use. This agent has now been documented to produce nephrotoxicity and renal failure with long-term administration. We collected 29 cases of semustine nephrotoxicity from the literature and six unpublished cases brought to the attention of the National Cancer Institute. Using these 35 cases as a data base, we have analyzed the incidence, dose and treatment duration relationships, clinical and histologic manifestations, and clinical course of semustine nephrotoxicity. In addition, we discuss the possible mechanisms of this nephrotoxicity based upon ongoing laboratory work. We conclude that there is a high risk of severe nephrotoxicity from semustine when the cumulative dose exceeds 1200 mg/m² and that there may be considerable delay in onset of the renal dysfunction. [Cancer Treat Rep 67:1105–1112, 1983]

Certain cancer chemotherapeutic agents such as cisplatin and streptozocin commonly cause immediate nephrotoxicity, and this is the dose-limiting feature of these two drugs. Some other agents cause nephrotoxicity only when administered over a long period (1). Semustine (methyl-CCNU) has now been recognized to be one of these drugs that can cause renal injury when large cumulative doses have been administered. Semustine remains an investigational drug, but it is being widely employed in the treatment of certain advanced cancers and as an adjuvant in the treatment of gastrointestinal cancers under protocols approved by the National Cancer Institute (NCI). Because of the importance of the recently recognized nephrotoxicity of semustine, we review this subject in all of its aspects. We use as a data base the published cases of this problem and the unpublished cases brought to the attention of the Division of Cancer Treatment, NCI. In addition, we discuss results of animal studies being conducted at the NCI to investigate the mechanism of semustine nephrotoxicity.

Background

Semustine is a nitrosourea analog that was synthesized at the Southern Research Institute as part of a lengthy search for effective antitumor agents in the nitrosourea class of compounds. It is structurally similar to two marketed nitrosoureas in clinical use, carmustine and lomustine. It differs from carmustine by the substitution of a cyclohexyl ring for one chloroethyl group and from lomustine only by the addition of a methyl group on the four position of the cyclohexyl ring.

In preclinical antitumor testing, semustine had marked effect against L1210 leukemia and produced cures of Lewis lung carcinoma, a notably drug-resistant cancer (2). It was also curative when used as a surgical adjuvant for line 26 colon carcinoma and B16 melanoma (2). These results generated interest in the drug, and clinical trials were initiated in 1971.

Although nephrotoxicity was observed in preclinical toxicology experiments (3,4), it was not seen in any of the clinical trials conducted in the early to mid-1970s (5–7). In late 1977, the NCI was notified of a case of possible nephrotoxicity from semustine, and a brief account suggesting such a relationship appeared in 1978 (8). Since these initial reports, other cases of semustine nephrotoxicity have been published (9–13). Many of these patients developed severe and irreversible renal failure. On two occasions the NCI sent letters to all investigators using semustine, asking for reports on any instances of possible nephrotoxicity. Responses on a total of nine unpublished cases were received. After discussions with the treating

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physicians, we judged three of these cases to have other, more likely causes for renal insufficiency; six cases of probable semustine nephrotoxicity remained. In addition, we contacted the authors of each of the published papers and obtained more detailed information and follow-up on their cases. We also obtained medical records of the three patients reported by Kundaria et al (12) that provided additional data compared to those published in their abstract. In the analysis, we did not include four patients (Nos. 12, 15, 16, and 18) receiving semustine reported by Schacht et al (10) and one patient (No. 4) reported by Nichols and Moertel (11), because we believed that the evidence for either significant renal dysfunction or a clear relationship to semustine was too tenuous. These exclusions left 29 published cases and six unpublished cases as the basis for our review.

Preclinical Toxicology

Studies of semustine toxicity in animals demonstrated that the kidneys were consistently affected in dogs, rodents, and monkeys (3,4,14). Monkeys treated with single oral doses of 1200–2400 mg/m^2 had severe and irreversible damage to the proximal convoluted tubules (14). At single oral doses of 1000–1200 mg/m^2 dogs had azotemia, but they did not have as severe abnormalities as those observed in monkeys (14). Mice given single ip doses of 63–189 mg/m^2 developed azotemia, with peak levels occurring 6 days after administration (4). At doses up to 126 mg/m^2 the BUN returned to normal by 21 days, but not if higher doses were used (4). Histologic examination revealed acute tubular necrosis that was most severe 6 days after drug administration; by 21 days cortical atrophy and fibrosis were noted (4).

These data suggested that nephrotoxicity might be observed in man, but there were obvious species and dose variabilities. No long-term dosing tests have been performed, so there is no preclinical information on chronic toxicity.

Incidence

Semustine has been in clinical trial for 12 years. It is not known how many patients have been treated with the drug in that time, but the number must be large. The NCI, as the sole supplier, distributed > 114,000 capsules of semustine in fiscal year 1981 alone (P. Vilk, personal communication). Despite solicitation of cases by the NCI on two occasions and newspaper publicity about the drug in the spring of 1981 (15), we have been able to define only 35 cases of nephrotoxicity.

As will be discussed below, no case of nephrotoxicity has been observed at a cumulative dose < 1400 mg/m^2. The rarity of the problem may be due to the fact that few patients reach this dose level. In a study (16) of 111 patients receiving semustine, only six (5%) received doses > 1000 mg (*not* mg/m^2). In another study involving 857 patients (11), only 22 (3%) received total doses > 1000 mg/m^2. However, three (14%) of these 22 patients developed renal insufficiency. If one selects as the denominator those eight patients in this study (11) who had a total dose ⩾ 1500 mg/m^2, then the incidence becomes 37.5% (three patients).

Micetich et al (13) tried to assess the incidence of nephrotoxicity in their patient series. Of 45 patients in the study, three had severe nephrotoxicity and four had elevated serum creatinine; overall, 15.6% of the patients had renal problems. If one uses as the denominator the 27 patients who received > 1400 mg/m^2, which was the minimum total dose where renal dysfunction was noted, then the incidence is 26%.

Most patients who receive semustine have short life expectancies and take the drug for only a few months. In addition, the myelosuppressive effect of the drug usually requires dose modification. If nephrotoxicity does not occur until doses of > 1400 mg/m^2 are reached, then it is not surprising that the problem was not noted in the early clinical trials. Only when the drug was used for many months in patients who had cancers with long survival times (9) or in the surgical adjuvant treatment of micrometastatic cancer (13) did the problem become apparent.

Dose and Age Relationships

Twenty-seven patients (Group 1) developed renal failure that resulted in death or in a need for dialysis (table 1). Eight patients (Group 2) had only moderate renal dysfunction that has required no treatment and appears not to be progressive. The median cumulative dose for all 35

TABLE 1.—Dose, age, and treatment duration relationships

Group*	No. of patients	Median total semustine dose in mg/m^2 (range)	Median age in yrs (range)	Median treatment duration in mos (range)	Median time to onset of nephrotoxicity in mos (range)
1	27	2320 (1400–5500)	21 (2–75)	22 (13–65)	24 (16–88)
2	8	1645 (1390–3360)	41 (33–52)	18 (12–32)	28 (11–45)
Totals	35	1950 (1390–5500)	32 (2–75)	21 (12–65)	27 (11–88)

* *Group 1:* renal failure usually resulting in need for dialysis or death; and *Group 2:* mild to moderate elevation of serum creatinine with no long-term change or symptoms.

patients is 1950 mg/m^2. The median cumulative dose of Group 1 is 2320 mg/m^2, with a range of 1400–5500 mg/m^2 (fig 1). In the report of Micetich et al (13), two patients who developed renal failure had the first indication of renal dysfunction at dose levels of 1400 and 1475 mg/m^2, but they received further semustine for total doses of 2000 and 1800 mg/m^2, respectively. For the purposes of this review we consider 1400 mg/m^2 to be the lowest dose at which nephrotoxicity has occurred. This lowest dose is different from that reported by Kundaria et al (12), because we were able to determine that one of these patients actually received 1900 mg/m^2 and not 1060 mg/m^2 as published. The median dose of Group 2 is 1645 mg/m^2, with a range of 1390–3360 mg/m^2. Group 2 had a lower cumulative dose ($P = 0.07$ by Wilcoxon rank-sum analysis, one-sided test), which may explain why the degree of renal injury was less severe in these patients.

One of the unpublished patients received the semustine iv. All of the other patients had the drug administered orally.

The patients with severe nephrotoxicity (Group 1) range in age from 2 to 75 years, with a median of 21 years. The median age in Group 2 is 41 years, with a range of 33–52 years.

Concomitant Therapy

Two patients reported by Schacht and colleagues (10) received carmustine before beginning semustine. One patient received 335 mg/m^2 and the other, 465 mg/m^2 (Patients 1 and 2). The amount of semustine given to these two patients was 4330 and 1715 mg/m^2, respectively. It is clear that the carmustine dose was relatively small, and the nephrotoxicity was related more to the semustine administered to these two patients. Additional information obtained on two of the patients reported by Kundaria et al (12) documented that both received some carmustine: one had 200 mg/m^2 before starting semustine and one had 450 mg/m^2 during 5 months after finishing 22 months of semustine. In this latter patient renal failure was recognized 2 months after the last carmustine dose. The total semustine doses administered to these two patients were 1900 and 2400 mg/m^2, respectively. As with the two patients reported by Schacht et al (10), the dose of carmustine was small in relation to that of semustine, and it is probable that the carmustine played little, if any, role in the development of nephrotoxicity.

In one unpublished case the patient received methotrexate with semustine. In one case reported by Nichols and Moertel (11), the patient was treated for 7 days with gentamicin 1 month after the first observation of an elevated serum creatinine. One month later the creatinine was higher. None of the other patients had known sequential or concomitant treatment with nephrotoxins.

Treatment Duration and Nephrotoxicity Recognition

The Group 1 patients were treated with semustine for 13–65 months (median, 22). The Group 2 patients were treated a median of 18 months (range, 12–32). Although the group exhibiting less severe toxicity was treated for a somewhat shorter time, the difference is not great.

The first indications of renal abnormalities appeared a median of 24 months (range, 16–88) after the start of semustine treatment in Group 1. In Group 2, the median is 28 months (range, 11–45). Abnormal renal function developed in 15 patients while they were receiving the drug. Nine of these patients had more semustine adminis-

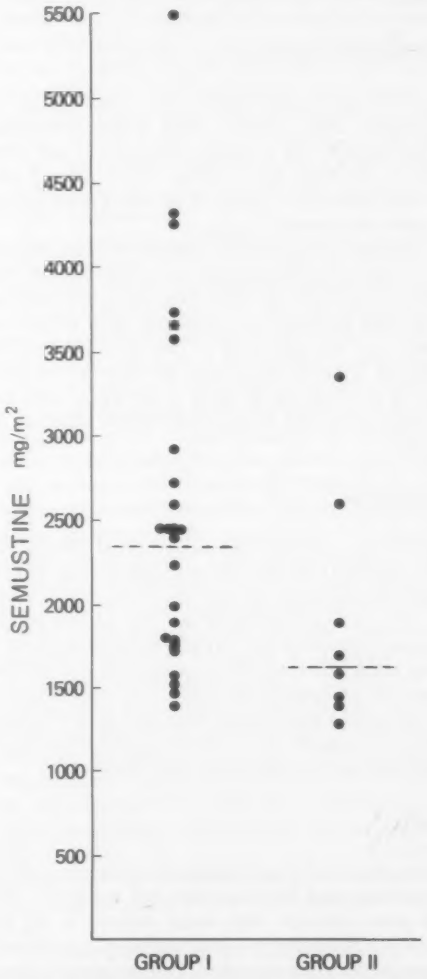

FIGURE 1.—Individual cumulative semustine doses among patients in Groups 1 and 2.

tered and six had the drug discontinued. Twenty patients (57%) had the indications of renal dysfunction appear from 2 to 49 months (median, 10) after discontinuing the semustine. As far as we are able to determine, no patient who had delayed onset of nephrotoxicity had other renal insults after semustine was stopped. This delay does not appear to have been due to a failure to obtain periodic renal function studies, because some patients had documented normal serum creatinines at the time of drug discontinuation and also months later. One of the patients initially reported by Kundaria et al (12) underwent a successful pregnancy and uneventful delivery 32 months after stopping the semustine and then developed her renal failure 17 months later (a total of 49 months after semustine).

Clinical Manifestations

The most frequent, and usually only, manifestation of nephrotoxicity was a slowly rising serum creatinine. Most patients had only sporadic urinalyses, if any were done at all, and these were normal. Some patients presented with anemia as a result of advanced renal failure and its secondary complications.

Small kidneys were seen in all patients in whom clinical testing for size or an autopsy was done. Harmon and colleagues (9) noted that the renal dimensions decreased in all six of their patients who developed renal failure. In addition, renal size decreased in two other patients (9) who received 776 and 1052 mg/m^2, but they did not have evidence of renal failure. In three of the six patients the renal outline continued to diminish despite cessation of semustine.

Clinical Course

Twenty-seven patients had severe renal failure. Of these, 20 required hemodialysis and three of them died of complications related to the dialysis. Three died of renal failure without having had dialysis. One patient underwent a renal transplant (9). All eight patients in Group 2 have had stable elevated serum creatinines and to date have required no specific treatment. The renal dysfunction in these eight patients has been mild with no serum creatinine > 1.8 mg/dl. In no case has discontinuation of semustine allowed reversal of the renal dysfunction.

Pathology

Eight patients had renal biopsies after the onset of renal dysfunction and five who died had autopsies. The autopsy gross findings were small kidneys in all instances, thus confirming the abnormalities noted clinically in some patients not autopsied. Tubular atrophy, hyalinization and sclerosis of glomeruli, and interstitial fibrosis were seen microscopically in each biopsied or autopsied case, although there was variability in the degree of these abnormalities. One patient in Group 2 died of his cancer and at autopsy had glomerulosclerosis that was characterized as "mild." No other patients in Group 2 have had histologic evaluation.

Electron microscopy was done in one case. The interstitium was composed of abundant collagen with no inflammatory cells. The proximal convoluted tubules had decreased microvilli with the cytoplasm containing decreased mitochondria and increased lysosomes. The sclerosed glomeruli had patent capillary loops and no cellular proliferation. Nuclei were prominent and elongated.

Comparison With Other Nitrosoureas

The other nitrosoureas in clinical use in the United States are streptozocin, chlorozotocin, carmustine, and lomustine. Streptozocin is the most nephrotoxic of the group (17). It can cause renal dysfunction after one dose, and up to 75% of patients will have nephrotoxicity of some degree with prolonged administration (17). The clinical manifestations are initially proteinuria and renal tubular acidosis, but the serum creatinine may rise with continued treatment. There is no cumulative dose relationship. Usually cessation of therapy allows reversal of the indicators of renal injury, but occasional cases progress to renal failure (17,18).

Chlorozotocin, the other nitrosourea-glucosamine compound in clinical use, is investigational and has not proven superior in any fashion to the other nitrosoureas. It too produces nephrotoxicity (19-21), but only isolated cases have been described, and it is not possible to determine an incidence or dose relationship.

Only three cases of nephrotoxicity from lomustine have been published (1). The cumulative doses were 1250, 1790, and 1940 mg/m^2. Since these are only anecdotal cases and no information is available about the total number of patients who have received > 1200 mg/m^2, it is not known whether lomustine is really less nephrotoxic than semustine or whether very few patients reach dose levels that produce risk.

Carmustine has rarely caused much renal toxicity. DeVita et al (22) noted unexplained BUN elevations in 10% of patients treated with this agent, but no instances of severe renal dysfunction have occurred in numerous subsequent studies. The report of Schacht et al (10) included four patients who received only carmustine (Patients 6, 11, 14, and 17). None had more serious renal dysfunction than a mildly elevated serum creatinine. One of these patients had a renal biopsy, and only mild interstitial and tubular abnormalities were seen (10). In contrast to the virtual absence of renal dysfunction from carmustine, there have been abundant cases of another form of chronic toxicity, interstitial pneumonitis and fibrosing alveolitis, especially when total drug doses have exceeded 1200-1500 mg/m^2 (23).

Mechanism of Nephrotoxicity

A specific mechanism of nephrotoxicity has not yet been implicated for any of the nitrosoureas, nor is it known if the different derivatives are likely to cause kidney injury by the same process. However, further insight into the mechanism(s) might help answer several intriguing questions concerning the current group of clinically important nitrosoureas. For example, why does semustine damage primarily the kidneys and not the lungs, whereas the reverse is true for carmustine? Also, among the nephrotoxic nitrosoureas, why do some (eg, streptozocin) appear to cause alterations in renal functions very acutely, whereas others (eg, semustine and lomustine) seem to cause delayed kidney damage? The available literature contains few hints to answer these questions. Moreover, the above differences derive principally from clinical observations, and the demonstration and experimental analysis of their counterparts in appropriate animal models has not yet been accomplished.

Experimental Models

To further explore the mechanisms and possible modifying factors of acute and chronic kidney injury by nitrosourea anticancer agents, NCI investigators recently have directed attention toward the development and characterization of suitable animal models (24). Initially, the focus has been on semustine, where attempts are being made to explore histopathologic correlations with sensitive in vitro and in vivo measures of renal function. Some early results from these studies are of interest. Rats treated with a single injection of semustine (240–960 mg/m^2) showed a dose-related decrease in the renal slice accumulation of *p*-aminohippuric acid (PAH). The accumulation of PAH was significantly depressed by 4 hours, reached a nadir within 12 hours, and remained depressed for at least 4 weeks. In contrast, the tubular transport of the organic base tetraethylammonium was not affected by semustine treatment. These findings suggest that the initial renal lesion may be occurring within a discrete region of the proximal tubule.

Changes in other measures of renal function (increased LDH excretion, alkalinuria, and decreased urine concentrating ability) were delayed from 1 to 6 days after semustine administration and in some cases progressed in severity throughout the 28-day duration of the experiment. The delay between the first evidence of renal damage (decreased PAH uptake) and the subsequent appearance of enzymuria, proteinuria, polyuria, and alkalinuria seems to correspond to a similar delay between the initial insult and the eventual development of cellular necrosis and other histopathologic changes (fig 2).

Chemistry and Metabolism

Could the mechanism of nephrotoxicity depend upon some unique structural characteristic and/or mode of biotransformation? Semustine, like most nitrosoureas, decomposes spontaneously in aqueous solutions to form carbonium ion alkylating agents as well as isocyanates that are capable of carbamoylation reactions (25). In this regard, the decrease in the tubular secretion of PAH by kidney slices following semustine administration was not seen when semustine was incubated directly with kidney slices (24). Thus, neither the parent compound nor a spontaneous breakdown product of the nitrosourea was acting as a direct inhibitor of the anion transport system.

The antitumor activity of semustine is believed to be due to the alkylation and cross-linking of nucleophilic sites in DNA by reactive electrophilic product(s) (26). It is conceivable that the numerous alkylation and carbamoylation (27) reactions of the degradation products of semustine also could result in toxic effects to normal host tissue. It is of interest that recent experiments have shown that both the carbamoylation of tissue proteins and alkylation of DNA by radiolabeled semustine were higher in kidney than in any other tissue (28). However, as yet, no clear-cut case can be made for either carbamoylation or alkylation as a basis for the nephrotoxicity of the nitrosoureas.

Most nitrosoureas including semustine are metabolized in the liver by a cytochrome P-450-dependent reaction to form hydroxylated derivatives. The hydroxylated products are formed rapidly and serve as immediate precursors to reactive degradation products (29). Hydroxylated metabolites of lomustine show differences in their therapeutic indices and in their alkylating and carbamoylating activities, depending upon the position of the hydroxyl group and steric configuration of the metabolite (30). Other recent studies (24) have shown that pretreatment with either an inducer (3-methylcholanthrene) or an inhibitor (piperonyl butoxide) of drug metabolism provided some protective effect against the nephrotoxicity of semustine. Moreover, pretreatment with a compound (buthionine sulfoximine) that decreased tissue glutathione levels also enhanced the nephrotoxicity of semustine. Therefore, it is conceivable that the nephrotoxicity of semustine might be mediated by a metabolically produced electrophilic metabolite or degradation product derived from a metabolite. It is interesting that pretreatment with SKF-525A, another type of drug metabolism inhibitor, has been shown in mice to inhibit the lethality and bone marrow toxicity, as well as the antitumor activity, of semustine (31). However, it should be noted that these pretreatments may modify the toxicity of semustine indirectly. For example, piperonyl butoxide is excreted to a large extent in urine and may therefore alter the renal handling and/or pharmacokinetics of semustine.

The susceptibility of the kidney to injury by certain drugs or preformed metabolites can be related to the high rate of renal blood flow, tubular concentrating capacity, or the reabsorptive and secretory processes of the proxi-

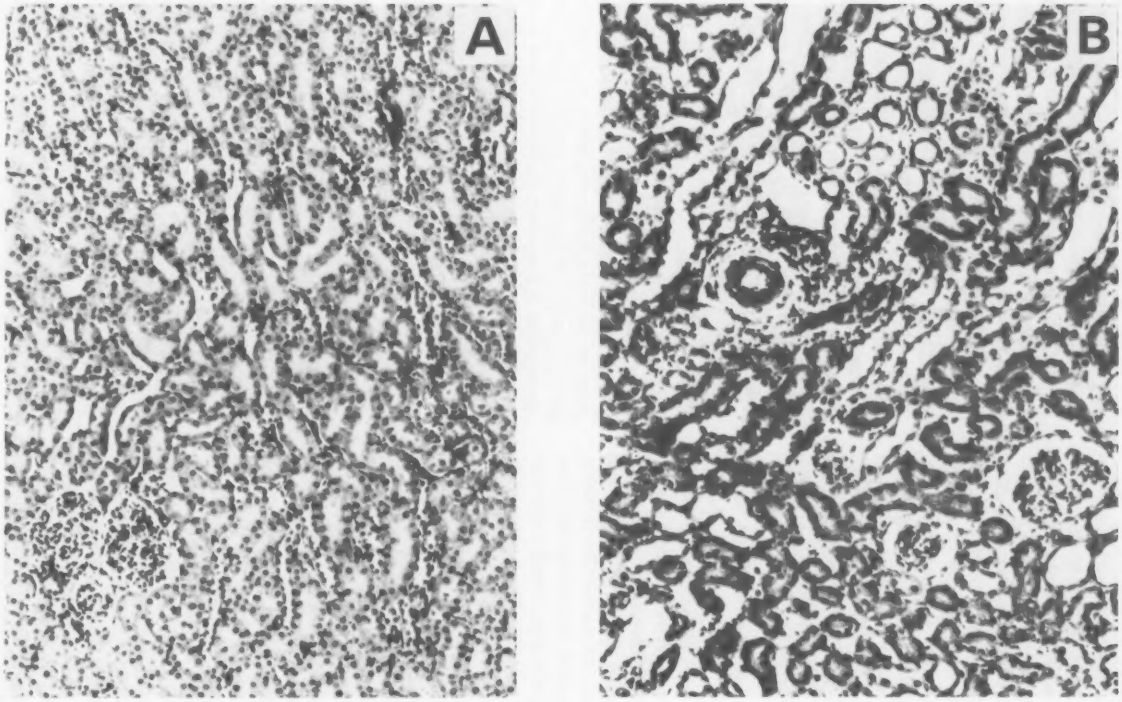

FIGURE 2.—Photomicrographs (original magnification, × 130) showing typical midcortical sections from (A) control rats (male, F-344) and from (B) rats receiving a single dose of 100 mg/kg of semustine sc, 21 days before they were killed. Kidneys of semustine-dosed animals (B) showed severe pathologic changes, including tubular cell degeneration, atrophy and necrosis, and a compensatory hyperplasia and cellular hypertrophy. Glomeruli also frequently were abnormal, with evidence of cellular swelling, degeneration, hyperplasia, and sclerosis. Also within the cortex there were focal accumulations of inflammatory cells as well as areas of early interstitial fibrosis. In the medullary regions (not shown) there were extensive hyaline casts and cellular debris within dilated collecting ducts and tubules.

mal tubules. Therefore, it may be important that urinary excretion is a major route by which semustine and its biotransformation products are cleared from the body (32). In this regard, the kidney has been shown to be exposed to the greatest tissue levels of semustine and its biotransformation products in Fischer 344 rats (28). More detailed and specific analyses of the formation, pharmacokinetics, and fate of such metabolites in the various tissues and in relevant models in vivo are needed.

Continuing studies are aimed at further elucidating the mechanism(s) of nitrosourea nephrotoxicity in this acute/subacute model as well as in chronic, repetitive-dosing models more closely mimicking the clinical situation. Using these models, it also may be possible to identify appropriate noninvasive tests of renal function to monitor patients receiving semustine or other potentially nephrotoxic nitrosoureas. Adequate monitoring might not only facilitate the detection and/or management of nephrotoxicity much earlier in the course of cancer treatment but also might help identify predisposing factors in susceptibility to these adverse reactions.

Nephrotoxicity Protection

A variety of means of protection against nephrotoxicity from cisplatin have been devised, the most successful being hydration with or without diuresis (1). No such investigations have been done for any nitrosourea, including streptozocin, the one that can frequently cause immediate nephrotoxicity. Clinical nephrotoxicity from semustine is sporadic and associated only with high cumulative drug doses. Because of these facts, plus the fact that so little is known about its mechanism, it is unlikely that a means of nephrotoxicity protection will soon be found. However, further investigations using animal models such as those described above may lead to new strategies useful in the clinic for treatment or prevention of the deleterious renal effect.

Conclusions

Semustine is clearly a nephrotoxic drug, but the incidence of nephrotoxicity is low because most patients do not receive cumulative doses > 1000 mg/m^2. However, for patients who do receive doses of ≥ 1400 mg/m^2, the incidence varies from 14% to 37.5%. Although few patients reach these dose levels, those who do are at high risk for nephrotoxicity. Thus, we believe that 1400 mg/m^2 is a relative dose limit for this drug, because all patients in our analysis had doses at or exceeding this point. A more conservative figure would be a limit of 1200 mg/m^2. A dose limit of 550 mg/m^2 has been similarly prescribed for doxorubicin because of the high risk of cardiomyopathy. Unless special circumstances dictate otherwise, we believe that widespread use of a dose limit for semustine of 1200 mg/m^2 is also desirable.

There has been a suggestion that children are more susceptible to semustine nephrotoxicity (13). This is not necessarily true, because the problem has occurred at all ages. The fact that the Group 1 patients were generally younger may indicate greater semustine sensitivity, but an equally plausible explanation is that they simply had cancers associated with longer survival that allowed them to receive more drug. Older adults are treated with semustine for more rapidly growing and lethal cancers such as melanoma and colon cancer and do not usually receive the high total doses where nephrotoxicity occurs. Since no comparison of separate age groups with identical total doses of semustine is available, one cannot be certain whether or not there is any age relationship to the nephrotoxicity.

The fact that one-half of the analyzed patients had a latency period of months to several years before renal dysfunction became evident is of particular importance. It indicates that serial monitoring of renal function while the patient is receiving semustine will not detect the problem early, thus allowing one to discontinue the drug and protect the patient from further problems. Use of the maximum dose as a stopping point is advisable, because of the severe nature of this complication. Of course, serial monitoring of the serum creatinine is still indicated because some patients may develop renal dysfunction at lower cumulative doses than 1200 mg/m^2, particularly if other renal disease or toxins are present. Also, any patient reaching the dose limit should then be monitored to detect delayed onset of nephrotoxicity.

The histology of semustine nephrotoxicity is nonspecific. Tubular atrophy, glomerulosclerosis, and interstitial fibrosis are abnormalities that can occur from multiple causes.

Streptozocin is the most nephrotoxic nitrosourea. Semustine now takes second place on the list. Little is known regarding the mechanism of nephrotoxicity from any of these drugs. It is indeed a paradox that a closely related compound such as carmustine has minor nephrotoxicity and major pulmonary toxicity, while the reverse is true of semustine (23).

Semustine has yet to be proven to have unique and meaningful efficacy for any cancer, and this is the reason that it is still an investigational drug. When using it, particularly in patients with a long predicted survival, one must balance the risk of long-term side effects such as nephrotoxicity and acute leukemia (33,34) with the possible benefit to the patient. Patients who receive more than a few doses of this agent must be monitored for renal dysfunction. If any more cases of nephrotoxicity are observed, the Investigational Drug Branch of the NCI should be promptly notified.

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Reproductive Potential of Vincristine-Treated Multinucleate Carcinoma Cells[1,2]

Gary S. Tennyson,* Barry J. Burbach, and Bernard P. Lane[3]

Multinucleate cells (MNC) form in a number of tumor cell lines treated with vincristine (VCR) and constitute the major difference between cell lines in which the affected cells survive VCR treatment and those in which the affected cells perish. We investigated the cell cycle traverse and proliferative potential of MNC which form among rat tracheal squamous carcinoma cells. Continuous-labeling curves for VCR-treated mononucleate and multinucleate cells were similar to those of untreated cells, and VCR-treated MNC survived for at least 7 days in culture. Observation of individual MNC, however, revealed no cytokinesis or continued proliferation. We conclude that although MNC arising after VCR treatment are capable of cell cycle traverse and prolonged survival in vitro, they are incapable of proliferation and, therefore, would not contribute to tumor regrowth. [Cancer Treat Rep 67:1113–1114, 1983]

While JB-1 ascites tumor cells (1) and HeLa cells (2) are irreversibly damaged and incapable of proliferation when treated with vincristine (VCR), Ehrlich ascites tumor cells may survive for several days after VCR treatment and traverse the G_1-phase to initiate DNA synthesis (3). Since multinucleate cells (MNC) commonly form in the Ehrlich ascites tumor (3,4) and in other cell lines treated with VCR (5,6), but not among treated HeLa or JB-1 cells, the capacity for multinucleation may underlie continued survival of cells. We examined the reproductive potential and cell cycle traverse of MNC appearing among rat tracheal squamous carcinoma cells treated in vitro with VCR. We found that these cells are capable of prolonged survival in cell culture and movement through the cell cycle, but are incapable of cytokinesis or proliferation and would not contribute to tumor regrowth.

METHODS

The RTC-9 cell line, its in vivo and in vitro cytokinetics, and cytokinetic and electron microscopic methods have been described (7).

VCR treatment.—Cell monolayers were treated for 18 hours with 20 ng/ml of VCR sulfate (Sigma Chemical Co, St. Louis, MO) added to the medium, rinsed three times with drug-free medium over 30 minutes, and then either fixed immediately or allowed to grow in drug-free medium for 72–96 hours before fixation. Continuous-labeling curves were determined over the interval of 48–96 hours after cessation of VCR treatment.

RESULTS

RTC-9 cells form small numbers of MNC spontaneously in monolayer culture (7% of cell production), but do not form viable MNC in vivo (7). Cultures treated with VCR for 18 hours and then exposed to drug-free medium for 72 hours form large numbers of MNC (79% of the cell population) in a time-dependent, but dose-independent (from 10 to 100 ng/ml), fashion.

Direct observation of 25 VCR-induced MNC (VCR-MNC) and 25 spontaneously occurring MNC (Sp-MNC) in low-density cultures revealed that none of these cells underwent cytokinesis over a period of 7 days. The cells either continued to form more nuclei, including micronuclei, or became spherical and floated off the culture surface.

Tritiated thymidine labeling of the MNC at any time after VCR treatment yielded a constant labeling index (table 1). In both VCR-MNC and Sp-MNC, all of the nuclei in the cells were labeled. Autoradiographic study of untreated mononucleate cells, VCR-treated mononucleate cells, Sp-MNC, or VCR-MNC which were labeled continuously demonstrated that all of the cell types tra-

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TABLE 1.—Cytokinetic parameters

Cell type	Time-to-maximum labeling (hrs)	Labeling index (%)	Growth fraction (%)	Cell cycle time (hrs)	S-phase (hrs)
Control mononucleate cells	12.4	41	98	21.3	9.0
VCR-induced mononucleate cells	12.4	42	94	22.4	10.0
Sp-MNC	13.0	41	98	22.4	9.4
VCR-MNC	12.0	43	88	23.5	11.5

versed the cell cycle and entered S-phase at similar rates, despite the lack of cytokinesis in the MNC (table 1). VCR-MNC exhibited a slight mitotic delay (reduced rate of labeling at 4-7 hours), which led to a somewhat longer cell cycle time.

A comparison of cellular cross-sections in electron micrographs demonstrated that tumor cells treated with VCR and then kept in drug-free medium for 72 hours contained a two- to three-fold greater number of microtubules than untreated cells, and that a mitotic tumor cell which was fixed immediately after 18 hours of continuous exposure to VCR still contained numerous microtubules radiating from a centriole toward condensed chromosomes.

DISCUSSION

Camplejohn et al (1) found that all JB-1 ascites tumor cells which were arrested in mitosis by VCR underwent necrosis. Metaphase-arrested cells were in S- and G_2-phases of the cell cycle at the time they were treated with VCR. Lengsfelt et al (2) followed VCR-treated HeLa cells by time-lapse cinematography and found that cells in late S- and G_2-phases were arrested in mitosis and became necrotic, while cells treated early in S-phase underwent a single abnormal mitosis to give rise to effete daughter cells. HeLa cells in G_1-phase at the time of VCR treatment were unaffected by the drug and maintained a nearly normal cell cycle time. These authors did not note the formation of MNC in their experimental systems.

In contrast, a number of other investigators (3-6) have found that significant numbers of MNC form after treatment with VCR. Szentirmay et al (4) found that multinucleate Ehrlich ascites tumor cells survived for up to 14 days in vivo, and Klein et al (3) noted that multinucleate Ehrlich ascites tumor cells were labeled with tritiated thymidine, suggesting that these cells traverse G_1-phase to initiate DNA synthesis. Klein (8) argued that the data demonstrate that cells which are affected by VCR survive and contribute to tumor regrowth, but he provided no evidence for the proliferative capacity of his MNC (8).

Multinucleate RTC-9 cells also survived for long periods in vitro after treatment with VCR and continued to traverse the cell cycle in a nearly normal fashion for at least 96 hours (> four cell cycles) (table 1), yet we could find no evidence for cytokinesis or continued proliferation of these abnormal cells. Either cytokinesis is a rare event in MNC or these cells have lost the potential for continued proliferation. The electron microscopic evidence that microtubules remain intact after drug treatment suggests that VCR may be exerting more subtle effects on subcellular organization and function.

Tumor cell lines differ in their responses to VCR (8,9). Some cells undergo multinucleation after treatment with the drug (3,5-7), while others may simply die (1,2). We have presented evidence that the surviving cells of a rat tracheal squamous carcinoma become multinucleate but do not proliferate after treatment with VCR. If MNC formed after exposure to VCR are always end-stage cells and if cells which are arrested in mitosis undergo necrosis (1,2), then further treatment of these apparently viable cells is unnecessary (9).

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Amsacrine Cardiotoxicity: Assessment of Ventricular Function by Radionuclide Angiography[1,2]

Daniel A. Vorobiof,* Mario Iturralde, and Geoffrey Falkson[3]

Serial assessment of ventricular function by means of a nuclear medicine technique was performed in six patients with malignant disease receiving chemotherapy with amsacrine. Two patients who received treatment long enough so that > 580 mg/m² of the drug was administered showed a significant decrease in left ventricular ejection fraction. Four patients who received total doses of 325–510 mg/m² of amsacrine did not experience significant change in their cardiac function. [Cancer Treat Rep 67:1115–1117, 1983]

Cumulative cardiotoxicity limits the total dose of some oncolytic agents such as the anthracyclines. Amsacrine (*m*-AMSA) is an acridinylmethanesulphonanilide compound not related to the anthracyclines. *m*-AMSA inhibits DNA polymerase in vitro, but the in vivo mechanism of action has not yet been clarified (1). Phase I and II studies in man showed that leukopenia was the major dose-limiting toxic effect of *m*-AMSA (2,3). Reports of cardiotoxicity possibly attributed to *m*-AMSA administration have been documented in the literature (4–7). Clinicians have explored noninvasive (electrocardiogram [ECG], echocardiogram, and radionuclide ventriculography) and invasive (cardiac angiography and endomyocardial biopsy) tests, which can predict clinical and pathologic cardiac dysfunction (8). Equilibrium radionuclide ventriculography using ECG gating has become an accepted method for noninvasive evaluation of left ventricular function and wall motion in patients receiving potentially cardiotoxic chemotherapy (5,9–11). This report is based on six patients treated with *m*-AMSA, where serial ECGs and radionuclide ventricular function tests were performed in order to predict the development of cardiotoxicity.

MATERIALS AND METHODS

Six male patients with a median age of 65 years (range, 58–70) were studied. Five of the patients had pleural mesothelioma and one had adenocarcinoma of the lung. They were evaluated prior to treatment by history, clinical examination, chest x-ray, cbc, and liver and kidney function tests. A baseline and follow-up ECG was performed every 3 weeks. Radionuclide ventricular function tests were performed as a baseline, repeated after three doses of *m*-AMSA, and at monthly intervals thereafter. *m*-AMSA (120 mg/m²) dissolved in 500 ml of 5% dextrose in water was administered as an iv infusion over 1 hour, every 3 weeks. The dose of *m*-AMSA was adjusted according to nadir cell counts. Multigated equilibrium radionuclide angiocardiography was performed using an in vivo rbc technique. Twenty millicuries of ^{99m}Tc pertechnetate was injected iv after a priming dose of 7.5 mg of stannous pyrophosphate. Data were acquired and processed with a digital gamma camera (Elscint Apex 415). An all-purpose parallel hole collimator was used. Imaging was performed in the 45° left anterior oblique projection with a preset program. Twenty-four frames were obtained for each cardiac cycle, allowing a minimum of 300,000 counts/frame. The left ventricular ejection fraction (LVEF) was computer-calculated automatically with a preset region of interest (ROI) program of the system. The reproducibility, validity, and accuracy of gated cardiac blood pool imaging and statistical analysis to evaluate observer and interstudy variances of the multigated blood pool imaging (as used in Pretoria) have been investigated and published (12,13).

RESULTS

Regular ECG follow-up failed to show any abnormalities. The normal LVEF in our laboratory is 55%. One patient, who received 580 mg/m² of *m*-AMSA, showed a

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TABLE 1.—Clinical summaries of patients included in the study

Patient No.	Age (yrs)	Diagnosis	Previous treatment	Risk factors*	Baseline LVEF†	Repeated LVEF	Total *m*-AMSA dose (mg/m^2)
1	58	Left pleural mesothelioma	No	No	64%	71%	325
2	64	Adenocarcinoma, lung	No	No	61%	60%	330
3	64	Right pleural mesothelioma	Radiotherapy, right hemithorax Doxorubicin (total dose, 530 mg) Procarbazine	Yes (previous treatment)	61%	52%	375
4	66	Right pleural mesothelioma	No	No	56%	58%	510
5	70	Left pleural mesothelioma	No	No	64%	42%	580
6	65	Right pleural mesothelioma	No	Yes (hypertension)	69%	42%	920

* Arterial hypertension, ischemic heart disease, diabetes mellitus, and previous doxorubicin treatment.
†Normal LVEF in our laboratory = 55%.

22% decrease of the LVEF (from 64% to 42%). A second patient, who received 920 mg/m^2 of *m*-AMSA, showed a 27% decrease (from 69% to 42%) of his LVEF. In this patient a risk factor (hypertension) also existed. A third patient, who had had previous doxorubicin treatment, showed a mild decrease (9%) in the LVEF after a 375-

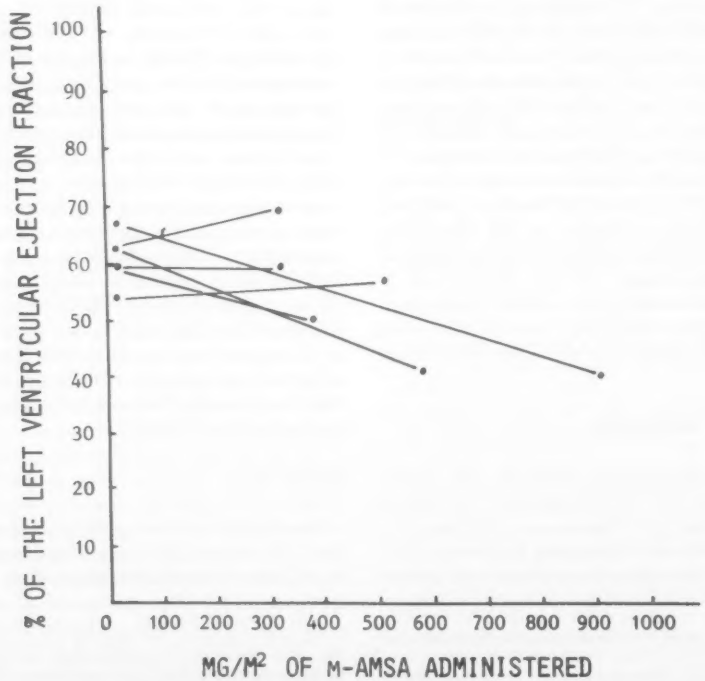

FIGURE 1.—Baseline and repeated radionuclide angiography in patients treated with *m*-AMSA.

mg/m² dose of *m*-AMSA. The remaining three patients did not show any change in the LVEF values (table 1 and fig 1).

DISCUSSION

There are a number of reports claiming cardiotoxicity due to *m*-AMSA (4–7). This is the first report of radionuclide ventriculography as a procedure to predict the cardiotoxicity of *m*-AMSA. A major decrease (> 15% to a final level of ≤ 45%) (14) in the LVEF values (determined by radionuclide angiocardiography) occurred in two patients receiving *m*-AMSA at doses > 580 mg/m², while a minor decrease was evident in one patient (who had previously been treated with doxorubicin) at a dose of 375 mg/m². Radionuclide ventriculography is of value in monitoring cardiac change in patients receiving *m*-AMSA and should be considered for patients to whom a large dose of *m*-AMSA is being given.

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Comparison of Vincristine and Vindesine in the Treatment of Inoperable Non-Small Cell Bronchial Carcinoma[1,2]

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Sixty-three patients with inoperable symptomatic non-small cell carcinoma of the bronchus were randomly allocated to receive either vincristine (1.4 mg/m²) or vindesine (3 mg/m²). These drugs were given weekly for four doses, then every 2 weeks for two further doses, and then continued monthly if there had been a response. Only five partial responses (> 50% reduction) were obtained with vindesine and none with vincristine. Disabling toxic effects occurred in 13 patients. This was more common with vindesine, but this group also received more prolonged therapy. Vindesine has modest activity against non-small cell carcinoma of the bronchus and may be more effective than vincristine, with similar toxicity. [Cancer Treat Rep 67:1119–1121, 1983]

Vincristine is a well-established chemotherapeutic agent with activity against a number of tumors. However, its activity against non-small cell carcinoma of the bronchus (NSCCB) is less certain. Brugarolas et al (1) reported a partial response rate of 17% overall, with the highest rate (33%) in adenocarcinoma. However, a subsequent study (2) confined to adenocarcinoma of the bronchus failed to confirm this. In three recent studies with vindesine (3–5), partial response rates were 17%–24%, and one of these studies (4) showed a trend in favor of adenocarcinoma. Toxicity in these studies was qualitatively similar to the well-known toxic effects of other vinca alkaloids. We present a prospective randomized trial to compare the efficacy and toxicity of the two drugs in NSCCB.

PATIENTS AND METHODS

Patients were eligible for the study if they were < 75 years of age, had inoperable NSCCB with measurable disease, and had significant symptoms due to primary or secondary tumor which were not considered amenable to radiotherapy. Patients who had recurrent or persistent symptoms after radiotherapy and had a further evaluable tumor site were also eligible, but those who had previously received any form of chemotherapy were not. Patients with only minimal symptoms were not studied.

After randomization, the drugs were given by bolus injection into a fast-running saline infusion. The doses were: vincristine, 1.4 mg/m² (maximum, 2 mg), and vindesine, 3 mg/m² (maximum, 5 mg). These were given weekly for four doses, then every 2 weeks for a further two doses. The patient was reviewed 2 weeks after the sixth dose (ie, 9 weeks after starting treatment), and treatment was continued at monthly intervals if there had been a response. Nonresponders received no further chemotherapy. Treatment was discontinued at any time if there was obvious disease progression or severe drug toxicity. If the total wbc count was between 2.0 and 3.0 × 10^9/L or the platelet count was between 80 and 100 × 10^9/L, treatment was given in half dosage. Below these levels, treatment was deferred for 1 week.

All patients had a full clinical examination, chest radiograph, and biochemical screen. Other staging investigations were performed only if clinically indicated. Limited disease was defined as tumor confined to one hemithorax and the ipsilateral supraclavicular lymph nodes, and extensive disease was defined as any progression outside this area. Tumor size was measured on the posteroanterior chest radiograph (excluding, whenever possible, areas of consolidation or collapse distal to the tumor) or by clinical measurement of metastases. Response was defined as either partial (PR) (at least a 50% reduction in two perpendicular measurements of the tumor sustained for 4 weeks, with no evidence of progressive disease elsewhere) or complete.

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No patient who entered the study was excluded from the analysis. Nonparametric statistical methods were used, ie, the chi-square test, the Fisher's exact probability test, or the Mann-Whitney U-test, as appropriate. All significance levels quoted are two-tailed.

RESULTS

Sixty-three patients entered the study and their characteristics and responses are summarized in table 1. All of the responses were apparent by the fifth week; no patient achieved a complete response. Five patients, all treated with vindesine, achieved a PR. All of these patients subsequently relapsed but their median survival (46 weeks) was longer than that of the nonresponders (13 weeks, $P < 0.01$, table 1). The 14% PR rate (five responses among 34 patients) with vindesine was not significantly greater than the 0% PR rate obtained with vincristine. The patients achieving a PR had a mean age 7 years less than that of the nonresponders ($P < 0.05$) and had a better initial KPS (range, 30%–80%). The response rate was not related to disease extent. The five PRs comprised two of the 26 patients with squamous cell carcinoma, two of the 17 with undifferentiated large cell carcinoma, and one of the 20 with adenocarcinoma. Only one of the patients achieving PR had a KPS of < 40%.

Transient leukopenia related to chemotherapy occurred in six patients, necessitating dose reduction in seven cycles, but there was no related infection. Four of these patients were among the 11 patients in the entire study who had previously received radiotherapy. The increased incidence of leukopenia in these patients was significant ($P < 0.02$). There were no episodes of thrombocytopenia. Mild paresthesia was common with both drugs during the first six cycles. Dose reduction was necessary in four patients. As the treatment intervals increased according to the protocol, the paresthesia improved in all but three patients. More severe neuropathy, both sensory and motor, was less common (three patients with vincristine and six with vindesine) but often slow to resolve despite stopping therapy. Severe constipation causing hospitalization or disruption of normal activities occurred in six patients. Altogether, four patients receiving vincristine and nine receiving vindesine suffered disabling toxic effects (severe paresthesia, weakness, or severe constipation).

TABLE 1.—Characteristics of patients in each treatment group

Characteristic	Vincristine	Vindesine
Total No.	28	35
Males/females	21/7	27/8
Mean age in yrs (range)	63.7 (51–75)	60.2 (30–75)
Median KPS* (range)	62% (30%–90%)	72% (20%–80%)
No. of patients with limited/extensive disease	14/14	14/21
Mean No. of cycles given (range)	4.2 (1–8)	5.9 (1–21)
PR	0	5
Survival (wks)		
Partial responders	—	46†
Nonresponders	14	12†
All patients	13	16

*KPS = Karnofsky performance scale.
†Survival of partial responders vs nonresponders; $P < 0.05$.

DISCUSSION

This is the first randomly allocated prospective study to compare vincristine and vindesine in NSCCB. Vindesine appeared to be more effective than vincristine. The 14% PR rate for vindesine is similar to the 17% PR rate reported by Østerlind et al (4), who used a higher dose (4–5 mg/m^2/week × 8), and it is less than the 22% and 24% PR rates reported by Gralla et al (3) and Luedke et al (5), respectively, who each used a dose similar to ours but given more frequently (3–4 mg/m^2/week × 10). However, we have confined our study to patients with significant symptoms, who are more likely to have extensive disease and a lower performance status, two factors which may reduce the response rate. Also, we included in our analysis the nine patients who received less than four cycles of vindesine; without these patients, the PR rate would have been 19%.

The results with vincristine are disappointing, with no PR. Brugarolas et al (1) used a lower dose of vincristine (1.5 mg irrespective of the patient's size) administered more frequently (weekly × 10) and achieved a PR rate of 17%. Most of these responses were in the patients with adenocarcinoma, but in a subsequent study confined to this cell type Brugarolas et al (2) failed to confirm the original finding. The response of adenocarcinoma to vindesine (one PR among 14 patients) was similar to that of squamous cell carcinoma (one PR among 14 patients), and is in keeping with others (3,5).

The major toxic effect of both drugs was neurologic, with an incidence similar to that found in other studies (1–4). The higher incidence with vindesine may be explained by the greater cumulative doses given, but the claim that vindesine would be less neurotoxic than vincristine (6) does not appear to be justified. We conclude that vindesine has modest activity against NSCCB and that it is more effective than vincristine, with equal toxicity.

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"Salvage" Radiation Therapy for Intrathoracic Small Cell Carcinoma of the Lung Progressing on Combination Chemotherapy[1]

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Thirty-two patients with small cell carcinoma of the lung were given chest radiotherapy to progressive intrathoracic tumor after failing chemotherapy. Two-thirds of these patients received split-course treatment at a dose of 4000 rad in 10 fractions. Sixteen of 25 evaluable patients (64%) had an objective response, but only five responders did not progress within the port during life. Median time to local progression was 16 weeks. Two patients, one of whom was given concurrent chemotherapy, survived > 18 months, and one is free of disease at 31+ months. Short-term palliation of chest disease and occasional long-term survival are possible with this regimen, although most patients will die with systemic disease within several months. Small cell carcinoma of the lung is less responsive to irradiation as second-line therapy than as initial therapy, but doses of ≥ 4000 rad can offer symptomatic relief in many cases and, rarely, survival beyond 18 months. [Cancer Treat Rep 67:1123–1126, 1983]

Small cell carcinoma of the lung (SCCL) is highly responsive to radiation therapy when given as initial treatment, with response rates in the range of 75%–90% (1,2). However, long-term survival in SCCL from radiation treatment alone is rare, and significant increases in the percentage of complete responders and 2-year disease-free survivors occurred only when combination chemotherapy was introduced. Many recent studies report treating patients with radiation therapy combined with chemotherapy. To date, however, there is only conflicting evidence that added chest irradiation increases the long-term survival rate beyond that achieved by combination chemotherapy alone (3–5).

At the National Cancer Institute, many SCCL patients have been initially treated with chemotherapy alone. This policy allowed us to study the therapeutic effects of chest irradiation given at the time of progressive intrathoracic disease. Our previous experience with various radiotherapy regimens demonstrated that prolonged local control was not achieved in patients treated with thoracic irradiation at the time of disease progression on chemotherapy. However, employment of higher radiation doses did appear to lengthen the time to local disease progression (6).

Since that earlier report, 32 additional patients with SCCL initially treated with chemotherapy alone were given radiotherapy at the time of progressive chest disease. Most of this group of patients were treated with higher-dose (4000 rad/10 fractions) split-course radiation therapy.

PATIENTS AND METHODS

The records of our 145 patients who began treatment for SCCL from November 1977 to December 1981 were reviewed in April 1982. During this time period, patients with limited-stage disease were randomized to receive combination chemotherapy with or without chest irradiation (3), while those with extensive disease were given four-drug (7) or cyclic alternating (8) combination chemotherapy without thoracic radiotherapy. Thirty-two patients initially treated with chemotherapy alone and subsequently given radiation therapy for progressive intrathoracic disease had evaluable tumor lesions on chest x-ray at the time they began irradiation. Other relapsing patients did not receive thoracic radiotherapy at the time of failure because of rapidly progressive systemic disease and/or lack of symptoms from intrathoracic tumor. Because of the retrospective nature of this study, more precise criteria which led to the decision to administer chest irradiation cannot be defined.

Patient characteristics are summarized in table 1. At the initiation of radiation therapy, 24 patients (75%) had demonstrable extrathoracic cancer in lymph nodes (eight

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TABLE 1.—Patient characteristics

Characteristic	No. of patients
Total	32
Evaluable	25
Completed therapy	24
Progressed during therapy	1
Median age in yrs (range): 56 (35–68)	
Sex	
Male	24
Female	8
Performance status*	
0–1	15
2–3	17
Initial stage	
Limited	12
Extensive	20
Detectable tumor at time of irradiation	
Intrathoracic only	8
Intrathoracic and extrathoracic	24
No. of chemotherapy regimens failed	
1	21
2	10
3	1
Concurrent chemotherapy	
Yes	14
No	18

* Eastern Cooperative Oncology Group criteria.

patients), bone (seven), liver (seven), central nervous system (seven), bone marrow (one), and brachial plexus (one).

Radiation therapy was delivered by a 6- or 10-mev linear accelerator via opposed anteroposterior-posteroanterior ports. Treatment volumes were determined through simulation and were shaped using custom-made focused blocks, and included the mediastinum in most patients. Ports were reduced or spinal cord blocks were added during treatment, as clinically indicated.

Twenty-three patients were treated with split-course 400-rad fractions to a 4000-rad total dose (400 daily × 5, 2-week break, 400 daily × 5). Six patients received split-course treatment with 200–300-rad fractions, to total doses of 3250–5400 rad. Three patients were treated continuously with 150–300-rad fractions, to total doses of 4200–5000 rad. Fourteen patients received new chemotherapy within 30 days of irradiation (11 received a single agent, and three received a combination regimen).

To be considered evaluable for response, a patient must either have completed the planned course of radiation therapy and have follow-up chest x-rays at least 4 weeks following completion of radiotherapy or have evidence of intrathoracic tumor progression during treatment. Seven patients did not meet these criteria. Four patients did not complete the planned course of therapy because of general deterioration (two patients), refusal (one), or death (one); two patients completed therapy but died of extrapulmonary complications within 4 weeks; and one patient did not return for follow-up chest radiographs.

A complete response was defined as the disappearance of all evaluable tumor. A partial response was defined as a $\geq 50\%$ diminution in the product of perpendicular diameters of measurable tumor or substantial reduction in size of an evaluable tumor agreed upon by two investigators. Responses were required to last for a minimum of 4 weeks. Local disease progression was defined as radiographic or bronchoscopic evidence of tumor progression or recurrence within the radiation port and was determined by simultaneous review of serial chest x-rays and port films. Times to local disease progression and death were calculated from the beginning of radiation therapy. The actuarial freedom from local progression was calculated using the method of Kaplan and Meier (9).

RESULTS

Twenty-five patients were evaluable for response and freedom from local progression. Fourteen partial and two complete responses were seen, for an overall objective response rate of 64% (50% among all patients who began irradiation). Responses were manifested by decreased size of pulmonary, hilar, or mediastinal masses in 12 patients and re-expansion of atelectatic segments of the lung in six. Two patients experienced clinical improvement in superior vena caval obstruction. The two complete responses were documented by chest x-ray and bronchoscopy in one patient and by chest x-ray alone in the other.

The association of several potentially influential factors with response is shown in table 2. There was a somewhat but not statistically significantly higher response rate for patients with good performance status and without evidence of extrathoracic tumor. The addition of chemotherapy (usually a phase I or II investigational agent) did not increase the response rate.

The 25 patients evaluable for local effects of treatment had actuarial freedom from local progression for a median of 16 weeks from the initiation of radiation therapy, as shown in figure 1. Despite their short survival, 16 of 25 patients (including 11 of 16 responders) eventually developed evidence of local progressive tumor. The actuarial median time to local progression was 15 weeks for responders and 17 weeks for nonresponders. Only two patients were at risk for disease progression beyond 30 weeks.

Median survival for all 32 treated patients was 15 weeks. For evaluable patients, median survival was 18 weeks for responders and 12 weeks for nonresponders. Both patients achieving complete response, who represent two of the eight patients who had no evidence of extrathoracic tumor at the time of irradiation, had prolonged survival. One patient died 21 months after chest radiotherapy alone (4000 rad/10 fractions) without local recurrence; the other is still alive and free of disease 31

TABLE 2.—Responses in evaluable patients

	No. of responses			
	Complete	Partial	None	% objective response
Overall	2	14	9	64
Performance status				
0–1	1	10	4	73*
2–3	1	4	5	50
Tumor				
Intrathoracic only	2	4	2	74*
Extrathoracic	0	10	7	59
Concurrent chemotherapy				
Yes	1	5	5	55*
No	1	9	4	71

*$P > 0.20$ by Fisher's exact test.

months after irradiation (5100 rad/17 fractions) with concurrent administration of a new combination chemotherapy regimen.

DISCUSSION

The major sites of relapse after chemotherapy for SCCL are in the initial sites of disease, particularly intrathoracic lesions (8,10,11). Our previous experience in using radiation therapy in this setting yielded an overall response rate of 52% and a median time to local progression of 13 weeks. Only three of 12 responders (25%) had no further local disease progression during life, and there were no survivors beyond 18 months. These patients were treated with a wide range of radiation doses (median, 3200 rad), but we did observe improved freedom from local progression in a small group of patients treated with a higher radiation dose of 4000 rad/10 fractions (6).

Since other investigators (1,12) have noted that a dose-response relationship exists for the treatment of SCCL with radiation therapy at the time of diagnosis, we thought it reasonable to employ this higher 4000-rad dose in a larger group of patients. Although a dramatically improved response rate or duration of freedom from local progression was not apparent compared to the earlier series, a positive trend was observed. The response rate was 64%, with a median time to local progression of 16 weeks. Five of 16 responders (31%) did not progress intrathoracically for the duration of their illness, and there were two patients with prolonged local control and survival beyond 18 months (21 and 31+). The latter case represents the only patient in our personal experience who has been potentially "cured" with

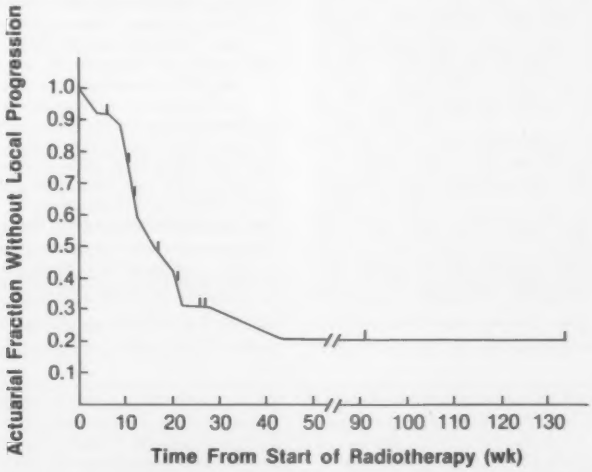

FIGURE 1.—Actuarial freedom from local disease progression in 25 evaluable patients irradiated for intrathoracic SCCL.

thoracic radiation therapy and chemotherapy after failure of primary treatment.

We continue to believe that aggressive doses of radiation produce the best responses in patients with thoracic relapse of SCCL. However, many patients cannot tolerate a protracted course of treatment. Most patients will have systemic tumor and will be receiving other chemotherapy which can contribute to radiation toxicity. Poor performance status and compromised pulmonary function can further reduce radiation tolerance. Thus, for short-term local palliation in patients with systemic tumor, 4000 rad via split course may be approaching the maximum dose that can safely be administered. When no systemic disease is present, it may occasionally be possible to produce more prolonged survival in patients with thoracic SCCL who fail chemotherapy. In these patients, radiation dosage should be pushed to higher levels if possible.

The lower response rate and shorter response duration achieved by salvage radiotherapy compared to initial radiotherapy suggest to us that small cell carcinoma cells may change their radiobiologic characteristics over time. SCCL cell lines grown in vitro sometimes develop new morphologic, biologic, and biochemical characteristics and resemble large cell undifferentiated lung carcinoma (13). Recently, these small cell lines "converting" to large cell carcinoma have been found to exhibit a significantly decreased sensitivity to the effects of radiation compared to classic small cell lines (14). It is interesting to speculate that this in vitro conversion of small cell lines to radioresistant large cell carcinoma may have clinical relevance.

The progression of SCCL following initial treatment is an ominous sign. Second-line single-agent chemotherapy produces responses of short duration in only 0%–36% of patients (15), and median survival from diagnosis of relapse was only 7–8 weeks in one large cooperative group study (16). Although our evaluable irradiated patients are obviously a highly selected group, local radiation produced objective responses in nearly two-thirds of them. We believe that substantial doses of radiation are required to achieve this effect. While impact on overall survival may be small, significant palliation of symptoms due to intrathoracic masses occurs more frequently than is customarily observed with chemotherapeutic management alone. Furthermore, a rare patient treated with salvage radiation therapy and second-line chemotherapy may achieve prolonged local control and survival, and local therapy for the patient with relapse of SCCL confined to the chest should be designed with this potential in mind.

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Phase I Trial of Cytarabine and Hydroxyurea[1,2]

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A combination of hydroxyurea (HU) and cytarabine (ara-C) can overcome ara-C resistance in vitro. To determine the pattern of toxicity of this combination, 22 patients with refractory leukemia and lymphoma were treated for 5 days with ara-C (100 mg/m²/day by constant infusion) and escalating doses of HU (0.375–1.77 g/m² every 6 hours). Hematologic toxicity was severe even at the lowest HU dose level. Skin and mucosal toxic effects were frequent but not dose-limiting. No novel types of toxic effects were observed. [Cancer Treat Rep 67:1127–1129, 1983]

Hydroxyurea (HU), by inhibiting ribonucleotide reductase and therefore synthesis of deoxycytidine diphosphate, decreases the intracellular dCTP pool (1). This results in decreased feedback inhibition of deoxycytidine kinase, permitting increased phosphorylation of cytarabine (ara-C) to its cytotoxic form, ara-CTP. The resulting increase in the ara-CTP pool and the decrease in the dCTP pool lead to enhanced incorporation of ara-CTP into DNA (2) and increased cytotoxicity (3). HU markedly improves the therapeutic ratio of ara-C against the murine L1210 leukemia in vivo (4) and increases the activity of ara-C against the HL-60 human promyeloblast cell line in vitro (3). This study was conducted to determine the pattern of toxicity produced by HU administered concurrently with a 5-day constant infusion of ara-C.

METHODS

Ten female and 13 male patients with leukemia or lymphoma who had received and failed all treatment of proven merit were entered in the study. The mean age was 41 years (range, 6.5–77). The patients were treated with a 5-day infusion of ara-C (100 mg/m²/day) and concurrently received HU (orally every 6 hours) to maintain cytotoxic concentration of both drugs. A loading dose of HU (1.33 × maintenance dose) was given at the start of the ara-C infusion. The initial HU maintenance dose was 0.375 g/m². This was escalated both within and between patients to 0.56, 0.75, 1.0, 1.33, and 1.77 g/m². HU doses were rounded to the nearest multiple of 500 mg. Patients were re-treated every 4 weeks.

RESULTS

Thirty-seven courses were initiated. Two courses were discontinued early due to skin rash; two others were not evaluable due to early deaths (Days 5 and 7). The pattern of toxicity associated with this treatment program is presented in table 1. Myelosuppression was severe at all dose levels. Only two patients had wbc count nadirs > 1500/mm³ (both patients had lymphosarcoma cell leukemia with initial wbc counts of 294,000 and 95,400/mm³), and only one patient had a platelet count nadir > 50,000/mm³. Wbc count nadir occurred on Day 11 and platelet count nadir occurred on Day 13. There was no difference in the degree or duration of hematologic toxicity as a function of the dose of HU over the range studied.

Intermittent nausea, with and without vomiting, was experienced regularly; however, the nausea was mild, usually started on Day 1 or 2, and seldom continued for > 3 days. In no case did nausea or vomiting continue beyond the infusion period. Few patients requested antiemetics and those who did were effectively treated with phenothiazines. Mucositis occurred in 19 of 34 evaluable courses and was greater than the Eastern Cooperative Onocology Group (ECOG) grade 2 criteria in 20% of the

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TABLE 1.—Toxicity of ara-C + HU as a function of HU dose

HU dose (mg/m^2/6 hrs)	No. of —		Hematologic toxicity*				Gastrointestinal toxicity†		
			Wbc count		Platelet count		Nausea and vomiting	Mucositis	Diarrhea
	Patients	Courses	Pretreatment	Nadir	Pretreatment	Nadir			
375	6	8	22.6 (0.5-300)	0.69 (0.1-49)	55.6 (4-321)	8.4 (1-50)	2 (1) 2 (2) 1 (3)	3 (1)	3 (1)
560	3	3	18.0 (4.2-94.4)	2.78 (0.3-47.6)	43.6 (21-180)	17.9 (6-20)	2 (1)	1 (1)	
750	4	9	7.0 (0.4-200)	0.28 (0.05-1.3)	30.8 (14-138)	16.0 (5-39)	5 (1) 1 (2)	5 (1)	2 (1)
1000	5	7	10.6 (3.4-80.7)	0.46 (0.3-1.2)	98.5 (14-322)	6.0 (3-24)	4 (1)	1 (1) 3 (3)	3 (1)
1333	3	3	4.3 (1.4-17.8)	0.18 (0.1-0.6)	49.5 (36-68)	12.2 (11-15)	2 (1) 1 (2)	1 (1) 1 (2) 1 (3)	0
1778	3	4	9.4 (3.7-87.9)	0.71 (0.6-1.2)	93.8 (65-236)	5.6 (4-9)	2 (1) 2 (2)	1 (1) 1 (2) 1 (3)	1 (2)

*Values = geometric mean (range), × 10^3 cells/mm^3.
†Values = No. of courses (grade by ECOG scale).

courses. The frequency and severity of mucositis appeared to increase with increasing HU dose, but this may be an artifact of the small number of evaluable courses at each dose level. Diarrhea was twice as prevalent in courses with mucositis as in courses without (six of 17 vs three of 16, respectively).

Skin toxicity manifesting as alopecia (two of two evaluable courses) and/or rash (15 courses in 12 patients) was also a frequent finding. The rash consisted of a bright-red maculopapular eruption, appearing between Days 4 and 7 and primarily involving the trunk and pressure points over the extremities. Palmar, plantar, and/or facial erythema and swelling were experienced by some. Desquamation of the involved area, with residual hyperpigmentation, sometimes occurred. Onset of rash was often heralded by stiffness and arthralgias of the small joints of the hands and feet. There was no evidence of hepatotoxicity.

Nineteen patients were evaluable for response. In one of 13 patients with circulating blasts, peripheral blood was cleared. One patient with acute myelomonocytic leukemia achieved a complete remission for 8 months, and a second patient with diffuse histiocytic lymphoma achieved a complete remission for 5.5 months. All other patients failed to respond.

DISCUSSION

Cellular resistance to ara-C may be due to decreased transmembrane transport (5), low levels of deoxycytidine kinase activity (6), high levels of deoxycytidine deaminase activity (7), high intracellular dCTP concentrations (6,8), rapid catabolism of ara-CTP (9), and/or altered sensitivity of polymerase to ara-CTP (10). One way to overcome ara-C resistance is to use massive doses of ara-C to enhance the transmembrane flux of ara-C and to raise the substrate concentration for deoxycytidine kinase (5,11). Another way is to use HU, an approach which is attractive in part because it affects several possible mechanisms of resistance simultaneously. By decreasing the concentration of dCTP, feedback inhibition of deoxycytidine kinase is diminished, resulting in greater phosphorylation of ara-C to ara-CTP (2). At the same time, a lower concentration of dCTP favors the binding of ara-CTP to DNA polymerase and its incorporation into DNA (2,12).

In this study, we examined the pattern of toxicity produced by the addition of HU to a 5-day constant infusion of ara-C. The pattern of toxicity (hematologic, gastrointestinal, and dermatologic) was that of HU superimposed on ara-C; no unexpected types of toxicity were observed. Gastrointestinal and dermatologic toxic effects were more frequent than single-agent studies would have predicted and were occasionally quite severe. The severity of hematologic toxicity was difficult to evaluate because the study population had had heavy prior treatment. However, myelosuppression, where it was evaluable, was not prolonged. Also, over the range studied, there was no correlation between dose of HU and nadir wbc or platelet counts. Little difference was seen in the toxicity produced by each dose level of HU. However, the nonhematologic toxicity of the ara-C and HU combination was more tolerable at the lower HU doses. The ara-C and HU combination represents a biochemically different approach to overcoming ara-C resistance that merits further clinical investigation.

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Phase II Study of Amsacrine Gluconate in Refractory Leukemia[1]

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Twenty-six adults with refractory leukemia were treated with amsacrine gluconate, a new formulation. There were two complete and two partial remissions. This preparation has no apparent advantage when compared with amsacrine lactate. [Cancer Treat Rep 67:1131–1132, 1983]

Amsacrine is active in refractory adult acute leukemia (1-6). It has previously been available for clinical trials as amsacrine lactate, with dimethylacetamide (DMA) as a solubilizing agent. Because questions were raised about the biologic activity and possible toxicity of DMA (7,8), it seemed desirable to test an alternative formulation which would be soluble without the addition of DMA. Amsacrine gluconate is such a formulation, which is reconstituted with sterile water for injection and requires no solubilizing agents. Bioequivalency studies done by Knutsen et al (9) show virtually identical plasma levels and concentration × time curves for the two formulations. Therefore, a phase II study of amsacrine gluconate was undertaken. The objectives were to determine the effectiveness of amsacrine gluconate in inducing complete remission (CR) in adults with refractory leukemia, and to evaluate patient tolerance of this new formulation. A preliminary report has been presented (10).

MATERIALS AND METHODS

Patients ≥ 15 years of age, in relapse after previous treatment for acute myelogenous leukemia (AML) or acute lymphoblastic leukemia (ALL), were eligible if they were not completely bedridden. Patients with blast phase chronic myelogenous leukemia (CML) were eligible if they had not had prior blast phase treatment. Eligible patients should not have received other therapy for at least 2 weeks and were not to receive concurrent systemic or intrathecal chemotherapy or radiotherapy.

Amsacrine gluconate was given as a 1-hour infusion at 120 mg/m^2 daily for 5 days. Two weeks after the beginning of the first course, a second course could be given for residual leukemia. Patients were to be treated until they achieved CR or until there was evidence of resistance to chemotherapy or recurrent leukemia after documented marrow hypoplasia. Before each course, bone marrow biopsy and aspiration were done. The dose was to be increased by 20% in the second and subsequent courses if the patient experienced no significant toxicity in the preceding course and if marrow hypoplasia was not achieved. The dose could be decreased by 20% for life-threatening infection or hemorrhage during the preceding course. Patients who received any treatment according to protocol and did not have a major protocol violation or refuse further treatment were considered evaluable. An adequate trial was defined as a minimum of two courses or achievement of CR with one course of treatment. CR were to be maintained with 50 mg/m^2 of amsacrine gluconate daily × 5 every 4 weeks until relapse. A CR required a normal bone marrow exam with < 5% blasts, a peripheral granulocyte count of at least 2000/mm^3, a platelet count of at least 100,000/mm^3, and no clinical leukemic infiltrates at the time of remission; for CR, the remission was required to last at least 2 weeks. A partial remission (PR) required at least some recovery of peripheral blood cell counts.

RESULTS

Twenty-six patients (13 males and 13 females) were entered in the study. Median age was 48 years (range, 20–70), and performance scores were 0 (seven patients), 1 (seven), 2 (eight), and 3 (four). Twenty patients had various forms of AML, one had ALL, and five had blastic CML. The patients had a median of two previous attempts at remission induction using other regimens (range, one to six). Inevaluable patients included one who refused further treatment, one who received concurrent chemotherapy along with amsacrine gluconate, and one

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TABLE 1.—Results for patients treated with amsacrine gluconate

Type of leukemia	No. of patients					
	Entered	Evaluable	Adequately treated	Hypoplastic	CR	PR
AML	20	19	13	15	1	2
ALL	1	1	0	0	—	—
Blastic CML	5	3	2	3	1	
Total	26	23	15	18	2	2

who received amsacrine lactate by mistake during part of his treatment. Evaluable but inadequately treated patients included four who received only one course without response and four with early deaths. Thirteen patients with AML were adequately treated; of those 13, one (8%) achieved a CR for 1 month (beginning on Day 68) and two achieved PR (table 1). Of two patients with blastic CML who were adequately treated, one achieved a CR, including reversion to a normal karyotype beginning on Day 44; this remission lasted 8 months. The two patients with CR responded after only one course of treatment. The PR were seen after two and three courses of treatment and lasted 43 and 68 days, respectively. The responders had had a median of 1.5 prior regimens, compared with a median of three prior regimens among the nonresponders. The median survival of the responders (158 days) was significantly longer than that of the nonresponders (44 days) ($P = 0.0135$). As expected, all adequately treated patients had severe blood cell count depression. Severe marrow hypoplasia or aplasia occurred in 18 patients after a median of two courses (range, one to three). Four of the five evaluable patients who did not become hypoplastic had had two courses.

Amsacrine gluconate was well-tolerated symptomatically; of 23 patients, six (26%) had nausea with or without vomiting, four (17%) had diarrhea, 16 (70%) had mucositis, seven (30%) had hair loss, seven had fever, and one had phlebitis which was attributed to treatment. Increases were seen in bilirubin (five patients, 22%), alkaline phosphatase (four), and SGOT (two). One patient had a transient supraventricular arrhythmia with each course of treatment. Questionably related findings included increased BUN (four patients), and paresthesia, ptosis, pruritus, edema, and myalgia in individual cases.

DISCUSSION

Amsacrine gluconate is a new formulation which has some antileukemic activity, as shown by remissions in refractory AML and blastic CML. Toxicity is similar to that seen with the DMA lactate formulation. Other investigators (1–6) have reported a CR rate as high as 29% in refractory AML using amsacrine lactate. In the absence of significant toxicity from the amount of DMA required for solubilization, amsacrine gluconate has no apparent advantage over amsacrine lactate.

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Mitoxantrone: Modest Activity in a Phase II Trial in Advanced Prostate Cancer[1,2]

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Thirty-seven patients with metastatic prostate cancer refractory to endocrine therapy were treated in a phase II trial of mitoxantrone. Starting doses were 12 and 10 mg/m² iv every 21 days for good-risk and poor-risk patients, respectively. Of the 35 evaluable patients, two had objective partial regression and five had stable disease. Response duration ranged from 7 to 17+ months. The drug was very well tolerated by these elderly patients; myelosuppression was the major toxic effect. We conclude that mitoxantrone has modest activity and acceptable toxicity in patients with advanced prostate cancer. [Cancer Treat Rep 67:1133–1135, 1983]

Mitoxantrone is a new anthraquinone derivative with significant antitumor activity in animal tumor systems including P388 leukemia, L1210 leukemia, B16 melanoma, colon carcinomas 26 and 28, and Lewis lung carcinoma (1,2). Reduced cardiac toxicity in animals compared to doxorubicin represents a potential advantage of this active DNA intercalator. Phase I studies of mitoxantrone disclosed an estimated maximum tolerated dose of 12 mg/m² of body surface area as a single dose repeated at 21–28-day intervals or 4 mg/m² of body surface area daily for 5 days repeated every 28 days (3,4). In general, the drug is well-tolerated, with myelosuppression being the dose-limiting toxic effect. It is not clear yet whether the drug is cardiotoxic in humans (5). Phase II studies have shown that the drug is active in patients with advanced breast cancer (6–8), acute leukemia (9), and lymphoma (9). Because of excellent patient tolerance, mitoxantrone would be particularly suitable for older patients. We now report the Southwest Oncology Group's experience using mitoxantrone as a single bolus every 3 weeks in men with advanced prostatic cancer.

MATERIALS AND METHODS

Thirty-seven patients with advanced adenocarcinoma of the prostate were studied. The median age was 65 years (range, 54–81). All patients had histologically verified prostate cancer with measurable or evaluable disease. Patients must have had and failed previous endocrine therapy. Other pretreatment eligibility criteria included: total wbc count $\geq 3000/mm^3$, platelet count $\geq 125{,}000/mm^3$, serum creatinine ≤ 2.0 mg/100 ml, bilirubin ≤ 2.0 mg/100 ml, and a performance status of ≤ 3 (Southwest Oncology Group criteria). All patients gave informed consent according to institutional guidelines.

Prior to therapy, patients were stratified as good- or poor-risk. Poor-risk patients had any of the following: age > 70 years, heavy prior chemotherapy or poor tolerance to prior chemotherapy, or prior radiation therapy to ≥ 25% of bone marrow-bearing areas. Mitoxantrone was administered in 100 ml of 5% dextrose in water as an iv infusion over 30 minutes. The starting dose for good-risk patients was 12 mg/m² every 3 weeks; poor-risk patients received 10 mg/m². Subsequent doses were reduced by 17% for wbc count nadirs of 1000–1999/mm³ and by 50% for wbc count nadirs of < 1000/mm³.

During the study, cbcs were obtained weekly. Tumor measurements, acid phosphatase, and renal and liver function tests were obtained prior to each treatment. Response criteria employed were those of the National Prostatic Cancer Project (NPCP) (10). Response duration was calculated from the date treatment was initiated.

RESULTS

Thirty-seven patients were entered into this trial (table 1). Two patients were unevaluable (one was lost to follow-up after first treatment and the other refused therapy after first treatment for reasons not related to drug toxicity). Most patients were ambulatory > 50% of their

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TABLE 1.—Patient characteristics

Characteristic	No. of patients
Total entered	37
Total evaluable	35
Performance status*	
0-1	17
2	9
3	11
Previous therapy	
Endocrine	37
Radiation	19
Chemotherapy	22
Doxorubicin	5
Sites of disease	
Bone only	23
Soft tissue ± bone	9
Visceral ± bone	5
Acid phosphatase	
Normal	4
Elevated	33
Good-risk	17
Poor-risk	20

* Southwest Oncology Group criteria.

waking hours. All patients had had disease progression during previous endocrine therapy. Twenty-two patients had received prior chemotherapy, including five who had had previous doxorubicin. The median number of prior cytotoxic agents received was one. Seven patients had received three or more prior drugs.

Response to treatment is shown in table 2. Seven of the 35 patients evaluable for response had objective regression by NPCP criteria, including two with objective partial remissions and five with stable disease, for an overall response rate of 20%. One patient with partial regression had measurable disease in supraclavicular and pelvic lymph nodes. The other patient, with bone disease, had complete pain relief and normalization of the acid phosphatase. Four of the five patients with stable disease had bone-only disease and the other had measurable lymph node involvement. Response duration ranged from 7 to 17+ months (median, 10). Four of the seven responding patients had received previous cytotoxic chemotherapy. All five patients previously treated with doxorubicin had progressive disease with mitoxantrone. Five of the seven responding patients were fully ambulatory (performance status, 0-1) at the time treatment was begun. Survival of the responding patients was 7+, 9, 10, 11+, 16, 18, and 19 months. Median survival of the nonresponders was 5 months (range, 2-27).

Mitoxantrone was very well tolerated by most patients (table 3). Patients received a median of five courses of drug. The major toxic effect was leukopenia, with 21 patients (58%) having total wbc count nadirs < 2000/mm^3. Of these 21 patients, 11 were stratified as poor-risk and received a starting dose of 10 mg/m^2. Three patients required dose escalations, while 11 others had dose reductions, usually in the range of 10% and usually only after several courses. Thrombocytopenia and nausea and vomiting were uncommon side effects of therapy. One patient with pre-existing diabetes mellitus and coronary artery disease died from refractory congestive heart failure after a total mitoxantrone dose of 60 mg. This patient had not received previous doxorubicin.

DISCUSSION

Chemotherapy has been of limited benefit to patients with metastatic prostate cancer (11). Several standard single agents have objective response rates of 10%-20%, with an additional 20%-40% of the patients demonstrating subjective responses or stable disease. Clinical trials are complicated by advanced patient age, difficulty in accurately determining response, lack of uniform response criteria, and treatment of patients with large tumor burdens. The development of new agents with acceptable toxicity is clearly needed.

The results of this trial indicate that mitoxantrone has modest activity against advanced prostate cancer. Seven of 35 patients responded, including five patients with stable disease. Because of the difficulties in assessing response in this disease, stable disease is an important category of response. Duration of survival in patients with stable disease is equivalent to that in patients with objective regression (12,13). Not surprisingly, most responses in this study were observed in fully ambulatory patients.

Mitoxantrone was very well tolerated in this elderly patient population. No patient refused therapy because of drug toxicity. The major toxicity was leukopenia, with more than one-half of the patients having wbc count nadirs < 2000/mm^3. Thus, the starting dose of 10-12 mg/m^2 every 3 weeks is appropriate for this group of patients.

TABLE 2.—Response to treatment

Response	Total No. of responses	Previous chemotherapy	Duration of response (mos)
Partial response	2	1	8, 10
Stable disease	5	3	10, 10, 17+, 7, 12
Disease progression	28	18	—

TABLE 3.—Toxicity (36 patients)

Toxicity	No. of patients (%)
Leukocyte count (cells/mm^3)	
> 3000	11 (31)
2000-2999	4 (11)
1000-1999	18 (50)
< 1000	3 (8)
Platelet count (cells/mm^3)	
> 100,000	30 (83)
75,000-99,000	4 (11)
50,000-74,999	1 (3)
< 50,000	1 (3)
Nausea and vomiting	
None	32 (89)
Minimal	3 (8)
Moderate	1 (3)
Severe	0 (0)
Congestive heart failure	1 (3)

The cardiac toxicity of mitoxantrone is not well-defined. In animal models the drug was less cardiotoxic than doxorubicin (2). Cardiac toxicity manifested by congestive heart failure has been observed in several patients treated with mitoxantrone, but these reports do not clearly implicate the drug as the etiologic agent (5). Most of these patients had previously received doxorubicin or had other risk factors for the development of heart failure. One patient in the present study died of progressive heart failure after receiving three doses (total, 60 mg) of mitoxantrone. This patient had symptomatic heart disease prior to mitoxantrone therapy. Whether mitoxantrone contributed to his death is speculative. We conclude from this trial that mitoxantrone has acceptable toxicity and modest activity against advanced prostate cancer. Further clinical trials of this agent are indicated.

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Phase II Trial of Aclarubicin in Advanced Breast Cancer: A Cancer and Leukemia Group B Study[1,2]

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Aclarubicin (aclacinomycin-A; ACM-A), an anthracycline antibiotic, was isolated from a culture filtrate of *Streptomyces galilaeus* in 1973 by Japanese investigators (1). The mechanism of action appears to be inhibition of RNA and DNA synthesis (Class II anthracycline) (2). Preclinical and clinical trials indicated that ACM-A had a broad range of antitumor activity, with less hematologic and cardiac toxicity than has been observed with doxorubicin or daunorubicin (3,4). This study evaluated the activity of ACM-A in advanced breast cancer.

MATERIALS AND METHODS

Thirty-three women with histologically confirmed adenocarcinoma of the breast were entered in the trial. Eligibility criteria consisted of the following: measurable disease, Cancer and Leukemia Group B performance score (PS) ≤ 3, prior treatment with no more than two standard chemotherapy regimens, < 550 mg/m^2 of doxorubicin, expected survival of at least 8 weeks, wbc count $\geq 4000/\mu l$, platelet count $\geq 100{,}000/\mu l$, bilirubin ≤ 1.5 mg/dl, and serum creatinine ≤ 1.5 mg/dl. All patients had an extent of disease evaluation, a 12-lead electrocardiogram, and a radionuclide left ventricular ejection fraction determination. Patients with clinically evident cardiac disease or an ejection fraction < 0.45 were ineligible.

ACM-A was administered as a 20–30-minute infusion at an initial dose of 100 mg/m^2 for good-risk patients (PS 0 or 1 and prior radiotherapy limited to $< 50\%$ of major bone marrow-containing skeletal area) and 80 mg/m^2 for poor-risk patients (PS 2 or 3 or extensive prior radiotherapy). Treatment was repeated every 3 weeks. Subsequent doses were escalated by 20 mg/m^2 (maximum dose, 120 mg/m^2) for nadir wbc counts $> 3000/\mu l$ and platelet counts $> 100{,}000/\mu l$ and were decreased by 20 mg/m^2 for nadir wbc counts $< 2000/\mu l$ or platelet counts $\leq 50{,}000/\mu l$. Either continuous cardiac monitoring or periodic electrocardiographic rhythm strips were taken during drug infusion and for 60–90 minutes after completion of the treatment. Cbc and platelet count were repeated weekly; serum liver function tests, creatinine, and measurable disease parameters were assessed every 3 weeks. An adequate trial consisted of at least two cycles (6 weeks) or rapid disease progression after one cycle at a dose producing a wbc count nadir $< 3000/\mu l$. Standard response criteria defined in previous trials were used (5).

RESULTS

All 33 patients entered in the study had received prior doxorubicin-containing chemotherapy. Patient prestudy characteristics and toxicity are detailed in table 1. Five patients had early death from progressive disease, five failed to meet eligibility criteria, and one was removed from the study early because of severe nausea and vomiting; all were excluded from the response analysis.

There were no responses among the 22 adequate trials. Ninety-one percent of the evaluable patients had received at least two courses of ACM-A. The dose was escalated in 14% of the patients and was reduced or delayed in 55% of the patients because of hematologic and/or gastrointestinal toxic effects. Hematologic toxicity was manageable, with no associated infections. There was one gastrointestinal bleed in one patient with drug-induced thrombocytopenia. One patient with severe nausea and vomiting required hospitalization for iv fluid replacement. Cardiotoxic effects were observed in one patient who had previously received 440 mg/m^2 of doxorubicin. This manifested as atrial premature

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TABLE 1.—Patient characteristics and toxicity

Characteristic	
Total No. of patients entered	33
Age in yrs	
Median	58
Range	31-71
Performance status	
Median	2
Range	0-3
% of patients	
Prior chemotherapy*	
1 regimen	30
2 regimens	63
(average No. of cytotoxic drugs: 4.8)	
Dominant disease site	
Soft tissue	39
Osseous	18
Visceral	42
No. of evaluable patients	25
Hematologic toxicity†	
Wbc count (cells/μl)	
2000-3000	9
1000-1999	6
< 1000	0
Platelet count (cells/μl)	
50,000-100,000	8
< 50,000	1
Nausea and vomiting	19
Diarrhea	5
Phlebitis	1
Cardiac arrhythmia	1

*2 patients with 3 prior regimens (improperly entered in the study) are excluded.

†Lowest count recorded.

contractions and multifocal premature ventricular contractions on an electrocardiogram taken 3 weeks after the first dose of ACM-A. A repeat ejection fraction was unchanged. No alopecia or hepatotoxicity was observed.

DISCUSSION

There were no responses in this phase II trial of ACM-A for advanced adenocarcinoma of the breast. Two-thirds of the patients had received two prior combination-chemotherapy regimens for metastatic disease and all patients were refractory to doxorubicin. We conclude that ACM-A in this dose and schedule is not active in this heavily pretreated patient population.

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Mitoguazone in Advanced Renal Carcinoma: A Phase II Trial of the Southwest Oncology Group[1,2]

William A. Knight, III,[3] Anibal Drelichman,[4] Carol Fabian,[5] and Ronald M. Bukowski[6,*]

A resurgence of interest in mitoguazone (MGBG) has followed the observation of acceptable toxicity when the drug was given at doses ranging from 500 to 600 mg/m^2 on a weekly schedule (1). Since the completion of that study by the Southwest Oncology Group (SWOG) (1), > 50 single-agent and combination trials using MGBG have been completed or are ongoing. Significant antitumor activity has been observed in patients with lymphoma and Hodgkin's disease (2). The evidence of antitumor activity in renal carcinoma in our phase I study (1) was the basis for this phase II trial.

PATIENTS AND METHODS

Ninety-five patients with pathologically documented renal carcinoma and measurable disease were entered in the study. Sixty-two of these patients had received no prior hormone therapy or chemotherapy. Other characteristics included a median age of 58 years and a performance status of 2.0 (SWOG criteria).

MGBG was given as a weekly iv infusion in 100 ml of 5% dextrose in water over ≥ 45 minutes. The starting dose of 600 mg/m^2 was increased by 100 mg/m^2/week in the absence of toxicity. A dose reduction of 100 mg/m^2 was required for grade 2 or 3 toxicity (SWOG criteria), and therapy was interrupted for grade 4 toxicity. Therapy was continued after all toxic effects were resolved.

A complete response was defined as complete regression of all measurable disease; a partial response was defined as a > 50% reduction of the product of the two longest perpendicular diameters of the measurable lesions. If hepatomegaly was chosen as a followable parameter, a decrease of > 30% in the sum of the measurements below the xiphoid process and both costal margins in the midclavicular line was designated as a partial remission. Patients were considered evaluable for response if they ceived two courses of MGBG and were followed for at least 4 weeks.

RESULTS

Eighty-seven patients were evaluable for response. Five patients had insufficient information for response evaluation, two refused further therapy, and one developed spinal cord compression after one course of therapy. One patient had a complete response of 46 weeks. Three other patients had partial responses lasting 33, 12, and 8 weeks. One of the partial responders had complete resolution of systemic symptoms which included fever and night sweats. Four patients had stable disease for 120, 24, 16, and 8 weeks. The remaining 79 patients had progressive disease.

Toxic effects were evaluable for 94 patients who received a median of three courses of MGBG (range, 1-67), and are summarized in table 1. Severe toxic effects were seen in seven patients, three with severe mucositis, three with anorexia, and one who required hospitalization because of vomiting. Severe toxicity tended to occur after four weekly courses of treatment. Other toxic effects are listed in table 1 according to SWOG criteria. Toxicity was reversible when the drug was withheld.

DISCUSSION

When given on a weekly schedule, MGBG does not have significant activity in patients with metastatic renal carcinoma. The 95% confidence limits are that the true response rate is between 0 and 9%. The low response rate is similar to that reported by others (3,4), and further trials using this schedule are not warranted in renal carcinoma. As seen in other trials, severe toxicity tended to be cumulative and may be averted by either a rest after four courses or a biweekly schedule.

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[2]Supported in part by Public Health Service grants CA-22433, CA-14028, CA-12644, CA-04919, CA-12014, and CA-32102 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services.
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TABLE 1.—Toxic effects of patients treated with MGBG

Toxic effect	No. of patients
Nausea	7
Vomiting	
< 6 times/day	24
≥ 7 times/day	7
Hospitalization secondary to vomiting	1
Anorexia	10
Diarrhea	14
3–4 stools/day, no dehydration	2
> 4 stools/day, iv hydration required	8
Bloody diarrhea	4
Mucositis	32
Ulcers, able to eat	21
Ulcers, unable to eat	11
Neuralgia	22
Circumoral paresthesia	11
Balanitis	1
Marrow suppression	11

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Clinical Trial of PALA and L-Alanosine in Advanced Colorectal Carcinoma[1,2]

Michael J. O'Connell,* Joseph Rubin, Allan J. Schutt, Charles G. Moertel, and Larry K. Kvols[3]

PALA, an inhibitor of aspartate transcarbamylase, causes decreased pyrimidine synthesis. L-Alanosine, an antibiotic which inhibits adenylosuccinate synthetase, prevents monophosphate synthesis and causes depletion of adenosine triphosphate pools. Both agents have been shown to have significant activity against murine tumor model systems (1,2). The combination of PALA plus L-alanosine has been shown to have marked synergistic cytotoxic activity against human tumor cell lines in a soft agar culture system at the Mayo Clinic (J. S. Kovach and M. M. Lieber, personal communication). Furthermore, definite therapeutic synergism with this combination in murine P388 leukemia resulting in 3-4 logs greater cell kill than was observed with either agent used alone has been documented (3).

We have previously observed little therapeutic activity when PALA (4) or L-alanosine (5) was used as a single agent in the treatment of advanced colon cancer. However, it was our hope that clinical therapeutic synergism would be seen using these drugs in combination.

We conducted a pilot study of PALA plus L-alanosine given in a 5-day schedule. The dose-limiting toxic effect was stomatitis, observed in five of eight patients treated at dose levels of 500 mg/m^2 of PALA and 60 mg/m^2 of L-alanosine. This report summarizes our experience with combined PALA plus L-alanosine in 30 patients with advanced colorectal carcinoma.

PATIENTS AND METHODS

All patients had histologic proof of metastatic colorectal adenocarcinoma, had a measurable indicator lesion, and received outpatient treatment.

PALA was given at a dose of 500 mg/m^2 by iv push over 2-5 minutes daily for 5 consecutive days followed immediately by L-alanosine at a dose of 60 mg/m^2 by iv push over 5-10 minutes daily times five, with courses repeated at 4-week intervals.

Objective tumor response was defined as a $\geq$ 50% reduction in the size of mass lesions or a $\geq$ 30% decrease in linear measurements if malignant hepatomegaly was the primary indicator lesion.

RESULTS

Thirty patients were entered in this clinical trial (table 1). A single objective partial tumor response of 16 weeks' duration was observed. Median time to disease progression was 8 weeks (range, 2-32).

Toxicity consisted primarily of stomatitis. This usually consisted of superficial erosion of the buccal mucosa lasting 5-7 days. However, two patients developed severe ulcerative stomatitis. Diarrhea was seen in seven patients and was severe in two of these. There

TABLE 1.—Patient characteristics

Characteristic	No. of patients (N = 30)
Median age in yrs (range): 63 (30-74)	
Sex	
Male	18
Female	12
Performance status*	
0-1	18
2-3	12
Sites of indicator lesions	
Liver	18
Lung	7
Abdominal mass	3
Lymph nodes	2
Prior chemotherapy	
Yes	14
No	16
Objective tumor responses	1 (3%)
Toxic effect	
Nausea	12
Vomiting	4
Stomatitis	18
Diarrhea	7
Skin rash	1

*Eastern Cooperative Oncology Group scale.

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was no myelosuppression with the exception of a single patient who had a wbc count nadir of 3000/mm^3.

DISCUSSION

This study has demonstrated lack of significant therapeutic activity of combination chemotherapy with PALA and L-alanosine on a 5-day iv treatment schedule at the maximal tolerable dose levels of each agent as demonstrated by a pilot study. Although it is possible that higher doses of PALA and L-alanosine given in combination might be associated with increased antitumor activity, dosage escalation beyond the levels employed was limited by significant ulcerative stomatitis. These results indicate lack of reliability of the in vitro soft agar studies and murine leukemia models used in predicting clinical response to this chemotherapy regimen in human colorectal carcinoma.

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Compilation of 1983 *Clinical Trials Summaries* published in *Cancer Treatment Reports*

Tumor	Drug	Dosage*	No. of evaluable patients	Response†	Page
Aerodigestive carcinoma	L-Alanosine	250 mg/m^2 iv over 10 mins on each of 3 consecutive days q 3 wks	26	NR	1047
Breast	Aclarubicin	80–100 mg/m^2 by 20–30-min iv infusion	22	NR	1137
	Thymidine + 5-FU	Thymidine: 9 g/m^2/infusion over 30 mins q 28 days 5-FU: 225–325 mg/m^2 by bolus injection q 28 days	5	1 PR	735
	Acivicin	12–15 mg/m^2 iv over 30 mins daily × 5 days q 3 wks	22	NR	843
	Amsacrine	200–250 mg/m^2/day × 3 q 3 wks	16	2 PR	599
	PCNU	75–100 mg/m^2 by 30-min iv infusion q 6 wks	15	NR	305
	Mitolactol	180 mg/m^2 orally × 10 consecutive days	22	NR	955
	Mitoxantrone	5 mg/m^2 by 30-min iv infusion	31	2 PR	1039
Cervix	AMSA	60–90 mg/m^2 diluted with 500 ml of D5W and infused iv over 1 hr	25	1 CR	197
Colorectal	Thymidine + 5-FU	Thymidine: 9 g/m^2/infusion over 30 mins q 28 days 5-FU: 225–325 mg/m^2 by bolus injection q 28 days	9	2 PR	735
	PALA + L-alanosine	PALA: 500 mg/m^2 by iv push over 2–5 mins L-Alanosine: 60 mg/m^2 by iv push 5–10 mins/day × 5	30	NR	1141
	Ftorafur	2.5 g/m^2/day × 5 by iv infusion over 1–2 hrs	36	3 PR, 1 CR	505
	Hycanthone	60 mg/m^2 by iv infusion × 20 mins/day on each of 5 consecutive days q 4 wks	30	NR	593
	5-FU + melphalan	5-FU: 50 mg/kg/4 wks Melphalan: 0.3 mg/kg 4 wks	14	NR	595
	Bisantrene	260–300 mg/m^2 iv q 3 wks	25	NR	307
Endometrial adenocarcinoma	Dianhydrogalactitol	60–75 mg/m^2/wk	17	1 PR	737
Esophageal	Etoposide	100–120 mg/m^2 by slow iv infusion on Days 1, 3, and 5 of each 21-day cycle	20	NR	397
Germ-cell	Medroxyprogesterone acetate	500 mg/m^2/day orally	20	NR	953
Upper gastrointestinal tract adenocarcinoma	Etoposide	100–120 mg/m^2/day by iv infusion on Days 1, 3, and 5	36	3 PR	509
Hodgkin's disease	Cyclophosphamide + doxorubicin + vincristine + prednisone		12	3 CR, 9 PR	739
Kidney adenocarcinoma	Lomustine + vinblastine + hydroxyurea + medroxyprogesterone acetate	Vinblastine: 5 mg/m^2 iv on Day 1 of each 28-day course Lomustine: 60 mg/m^2 orally on Day 2 Hydroxyurea: 400 mg/m^2 orally q 12 hrs on days 3–14 Medroxyprogesterone acetate: 1 g/wk im starting on Day 1	26	3 PR	741
Leukemia	Maytansine	0.6 mg/m^2 by rapid iv infusion	15	NR	1045
Lung	Vindesine	3 mg/m^2 × 6 wks	48	9 PR	1041
Non-small cell	Aziridinylbenzoquinone	30–35 mg/m^2 by iv infusion in 100 ml of NS over 30 mins q 21 days	74	4 PR	95

Compilation of 1983 *Clinical Trials Summaries* published in *Cancer Treatment Reports* (continued)

Tumor	Drug	Dosage*	No. of evaluable patients	Response†	Page
	Bisantrene	260 mg/m^2 dissolved in 500 ml of D5W and infused over 2 hrs through peripheral vein	26	NR	841
	PCNU	100–125 mg/m^2 by slow iv infusion over 20 mins q 6 wks	17	NR	837
	ICRF-187	1500 mg/m^2/day by rapid iv infusion over 30–60 mins for 3 consecutive days	25	NR	311
	Cisplatin	50 mg/m^2 on Days 1 and 8 q 28 days	145	19 PR	399
	Bisantrene	260 mg/m^2 iv in 500 ml of D5W over 60 mins	20	NR	597
	4'-Epi-doxorubicin	65–85 mg/m^2 iv q 21 days	34	1 PR	591
Small cell	Etoposide	140 mg/m^2 iv	25	NR	951
	Mitoxantrone	12 mg/m^2 by 30-min infusion in 150 ml of D5W q 3 wks	54	2 PR	403
Lymphoma	Aziridinyl-benzoquinone	30 mg/m^2 in 500 ml of NS over 1 hr iv q 28 days	19	1 CR	507
Melanoma	Bleomycin + carmustine + vincristine + dacarbazine	Bleomycin: 30 units sc Carmustine: 75 mg/m^2 iv Vincristine: 1 mg/m^2 iv Dacarbazine: 1 mg/m^2 iv	14	1 PR	947
	Vindesine	3 mg/m^2 by continuous infusion in NS over 24 hrs	15	NR	839
	Corynebacterium parvum + surgery	4 mg/m^2/wk × 6, monthly × 6, then q 6 mos up to 5 yrs or relapse	34	24 CR	191
Myeloma	Acronine	200–500 mg/m^2/day orally	16	NR	93
Ovarian	Phenesterin	80 mg/m^2 orally twice/wk	37	1 PR	601
	Spirogermanium	80–120 mg/m^2 by iv drip over 30 mins every other day	17	NR	193
	PCNU	75–100 mg/m^2 q 6 wks	14	NR	511
Renal cell	Mitoguazone	600 mg/m^2/wk	87	1 CR	1139
	Amsacrine	60–120 mg/m^2	42	NR	1043
Sarcoma	Maytansine	0.6 mg/m^2/day × 3 consecutive days q 3 wks by rapid iv infusion	15	NR	401
Testicular	AMSA	100 mg/m^2/day × 3–4 days	6	NR	309
	AMSA + cisplatin	AMSA: 100 mg/m^2/day × 3 days Cisplatin: 20 mg/m^2/day × 5 days	3	NR	309
Transitional cell carcinoma of urothelium	Amsacrine	90 mg/m^2 iv	15	NR	845
Uterine cervix	Yoshi 864	1.5–2.0 mg/kg/day × 5 by slow iv push q 6 wks	18	NR	195

*D5W = 5% dextrose in water; NS = normal saline.

†NR = no response; PR = partial response; CR = complete response.

Effect of Disulfiram on Cyclophosphamide Toxicity: A Clinical Trial[1]

Cyclophosphamide (CTX) is the most commonly prescribed alkylating agent in clinical medicine. An important dose-limiting toxicity is hemorrhagic cystitis. The causative agent of this untoward effect has recently been identified to be acrolein, a toxic by-product of CTX metabolism (1,2). We have recently reported that prior or concurrent administration of disulfiram (DSF) successfully prevents CTX-induced bladder injury in mice (3,4). Furthermore, in mice harboring L1210 leukemia, DSF appeared to have no adverse effect on the oncolytic effect of CTX, but concurrent treatment did appear to prolong the CTX-induced granulocytopenia (4). Accordingly, Habs et al (5) had previously demonstrated that DSF administration reduced the acute LD50 value for CTX in male Sprague-Dawley rats. Nevertheless, it is probable that the active metabolite of DSF, diethyldithiolcarbamic acid, mediates its uroprotectant effect by binding covalently with the toxic metabolite of cyclophosphamide, acrolein. The mechanism for the prolonged granulocytopenia in tumor-bearing (L1210) mice receiving the combined therapies remains unresolved. DSF is known to inhibit acetaldehyde dehydrogenase, an enzyme involved in the metabolic degradation of active cyclophosphamide intermediates, and perhaps the prolonged granulocytopenia observed reflects greater activity (toxicity) due to a persistence of these active metabolites. Nevertheless, in additional preclinical experiments in our laboratory, the drug combination yielded no additional bone marrow toxicity (by bone marrow colony studies) when compared to CTX alone.[2] Long-term DSF use has been associated with peripheral neuropathy. Clinically, however, DSF is utilized in the treatment of alcoholism, a problem involving a population susceptible to neuropathy de nova. No other untoward reactions have been associated with DSF use, and it was therefore predicted that the combination of CTX and DSF would not produce significant toxic effects. With respect to the prolonged granulocytopenia in the murine tumor (L1210) model, however, we felt obligated to introduce the combination to clinical use by careful phase I evaluation to assess the possible augmentation of CTX toxicity by DSF.

Eighteen patients were asked to participate in the study. Each patient received CTX by iv bolus injection every 3 weeks. The dose of CTX was initially 350 mg/m^2 and was escalated by 350 mg/m^2 at each 6-week interval if the nadir and pretreatment wbc counts were > 2000 and 4000, respectively. With every other CTX treatment, 500 mg of DSF was given orally 2 days before, the day of, and 4 days after injection. All patients were carefully and repeatedly instructed not to consume alcohol in any form during this phase of the trial. Care was also taken not to enroll patients with potential compliance problems. Cbcs, urinalysis, and serum chemistries were obtained at weekly intervals.

Of the 18 patients enrolled in this study, 15 were evaluable (table 1). Three patients were not evaluable because of rapidly progressive disease. Hematuria associated with CTX, as determined by clinical history and urinalysis, was not observed in any patient. Nadir wbc counts (table 1) and platelet counts (data not shown) were not different in magnitude or duration after CTX alone or after the CTX-DSF combination. The only apparent toxic effect for which the combination was worse was nausea. In three of the 15 patients, nausea (but not emesis) was greater after the CTX injection when DSF was administered concurrently. In one patient, DSF prior to CTX injection resulted in nausea, and this was exacerbated after CTX injection. This patient did not have nausea when treated with CTX alone.

This trial suggests that at the CTX doses studied, the addition of DSF does not add significant toxicity. In light of these observations and the very impressive bladder protection demonstrated in mice (2,3), we suggest that a subsequent clinical trial in patients receiving high-dose CTX, such as bone marrow transplant recipients [in whom hematuria is frequent (6) and fatal hemorrhage has occurred] would be reasonable.

[1]Supported by Public Health Service grant CA-02543 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services. W. B. Ershler is the recipient of an American Cancer Society Junior Faculty Fellowship.

[2]Gamelli RL, Ershler WB, Hacker MP, et al. Cyclophosphamide myelotoxicity is not increased by disulfiram. Submitted for publication.

TABLE 1.—CTX-DSF clinical trial

Patient No.	Age (yrs)	Sex	Tumor site	CTX (mg/m^2)	Wbc count ($\times 10^3/mm^3$)					
					CTX			CTX + DSF*		
					Before	After	Change†	Before	After	Change†
1	58	F	Ovary	350	6.3	2.7	3.6	5.1	0.2	4.9
				350	10.0	3.7	6.3	7.9	1.5	6.4
2	29	M	Wilms	700	5.4	1.6	3.8	6.1	1.6	4.5
				700	4.2	1.1	3.1	7.6	ND‡	—
3	75	M	Colon	350	7.9	7.4	0.5	9.5	8.5	1.0
4	42	M	Colon	350	4.7	ND	—	6.6	5.5	1.1
				700	5.8	2.7	3.1	—	—	—
5	73	M	Larynx	350	10.5	10.1	0.4	8.5	6.8	1.7
				700	8.0	7.7	0.3	—	—	—
6	65	M	Pancreas	700	7.1	5.3	1.8	6.4	ND	—
				1050	6.9	6.9	0	6.6	4.1	2.5
				1400	9.2	3.4	5.8	5.7	3.2	2.5
7	45	M	Lung	700	7.5	5.2	2.3	8.8	5.2	3.6
				1050	9.8	5.3	4.5	9.2	3.4	5.8
8	65	M	Bladder	700	18.0	10.0	8.0	12.3	12.3	0
9	53	M	Colon	700	5.9	4.7	1.2	ND	—	—
10	64	M	Lung	700	6.2	5.4	0.8	5.1	4.8	0.3
				1050	5.9	3.2	2.7	3.8	3.2	0.6
11	53	M	Prostate	700	14.0	ND	—	14.0	8.7	5.3
12	42	F	Ovary	1050	4.1	3.0	1.1	5.2	1.7	3.5
13	65	F	Lung	700	16.8	8.8	8.0	17.2	16.5	0.7
14	59	F	Lung	700	8.0	8.0	0	11.6	7.0	4.6
				1050	7.0	4.8	2.2	7.6	6.3	1.3
15	66	M	Esophagus	700	9.8	8.7	1.1	9.3	8.3	1.0

* DSF (Ayerst) given at a dose of 250 mg orally twice daily 2 days before, the day of, and 4 days after the CTX injection.

†The change in wbc count from pretreatment level to the nadir (posttreatment) level. No significant difference was noted when CTX (alone) cycles were compared with CTX-DSF cycles. Mean changes ± SD were: CTX alone, 3.0 ± 2.4; CTX-DSF, 3.1 ± 2.0.

‡ND = not done.

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Hairy Cell Leukemia Responsive to Chemotherapy With Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine (ABVD)

Hairy cell leukemia is characterized by pancytopenia, splenomegaly, tartrate-resistant acid phosphatase-staining hairy cells in the peripheral blood, and leukemic infiltration of the bone marrow. Although 20% of patients have enlarged lymph nodes, prominent lymphadenopathy is rare. Here we report a patient with progressive hairy cell leukemia with massive para-aortic lymphadenopathy and malignant ascites who responded to treatment with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) (1).

CASE REPORT

A 58-year-old man presented in December 1977 with hepatosplenomegaly, pancytopenia (hematocrit, 25%; leukocyte count, 2400/mm^3; and platelet count, 58,000/mm^3), tartrate-resistant acid phosphatase-staining hairy cells in the peripheral blood, and leukemic infiltration of the bone marrow. After his 3-kg spleen was removed, the hematocrit and platelet count became normal. Thirteen months later, anemia and thrombocytopenia recurred. Five months of parenteral androgens improved his hematocrit to 36% and platelet count to 110,000/mm^3, but the leukocyte count rose from 14,000 to 44,000/mm^3. He was subsequently treated with etiocholanolone and prednisolone for 10 months, with worsening pancytopenia complicated by bleeding and infection. He next underwent leukapheresis 11 times; however, he became cachectic and developed massive para-aortic lymphadenopathy and a peritoneal exudate containing hairy cells.

In view of his rapidly progressive disease, the patient was started on ABVD therapy in July 1980, at a 45% dose reduction because of his moribund condition and pancytopenia. After the first month of treatment, the ascites decreased, and he was able to walk with assistance. Ascites disappeared after 3 months of chemotherapy, and the patient resumed normal activities. Vinblastine and bleomycin were discontinued at this time because of peripheral neuropathy and pulmonary interstitial fibrosis; doxorubicin and dacarbazine were continued for 1 year, at which time the leukocyte count was 4500/mm^3 with 10% leukemic cells. Ascites and para-aortic lymphadenopathy disappeared. His recent course has included bacterial pneumonia, herpetic stomatitis, and coccidiomycosis (complications of continued immunoincompetence). Now, 3 years after starting ABVD treatment, the marrow infiltration remains unchanged, but the hematocrit is 44% without transfusion, the platelet count is 500,0000/mm^3, the leukocyte count is 8700/mm^3 with 2% hairy cells, and the patient feels well.

DISCUSSION

Hairy cell leukemia generally follows a chronic course, with a median survival of about 5 years. Initial management is conservative, but patients with hypersplenism experience an improvement in blood cell count and prolonged survival following splenectomy. Patients who fail to respond to splenectomy or who develop progressive disease following splenectomy pose a difficult problem. Until recently, chemotherapy was considered contraindicated in hairy cell leukemia because of the poor bone marrow reserve and the increased risk of infection. For this reason, we attempted to treat our patient with androgens, etiocholanolone, and leukapheresis, which have

been reported to be beneficial in some patients. However, when the patient's disease continued to progress and he developed massive para-aortic lymphadenopathy, malignant ascites, and clinical deterioration, we decided to resort to chemotherapy.

Improvement in the peripheral blood cell count and decreased marrow infiltration with hairy cells have been reported with daily chlorambucil, but this generally requires 6 months before benefit occurs (2). Ablative chemotherapy with high-dose zorubicin (3) has led to complete remission in hairy cell leukemia, but vigorous supportive therapy was needed during the period of marrow aplasia. A complete remission lasting > 4 years was obtained after chemoradiotherapy, followed by identical twin bone marrow transplantation (4), a treatment not readily available to most patients with hairy cell leukemia. Occasionally, patients have also benefited from vincristine and prednisone alone or in combination, anthracyclines alone or in combination, and combinations containing cyclophosphamide or cytarabine (3). We chose ABVD because of the absence of severe marrow aplasia with this therapy in patients with Hodgkin's disease who have undergone prior chemotherapy with mechlorethamine, vincristine, prednisone, and procarbazine (MOPP) and radiotherapy (1). This drug program contains an anthracycline compound as well as a vinca alkaloid, both having been associated with response in some patients with hairy cell leukemia (3). The chemotherapy was well-tolerated and rapidly resulted in clinical improvement which has been sustained for > 3 years.

An interesting feature of this patient's disease was the massive para-aortic lymphadenopathy and ascitic fluid containing hairy cells. While lymphadenopathy may be seen in 20% of patients with hairy cell leukemia, it is usually minimal. Moderate retroperitoneal adenopathy can be found in 20% of patients undergoing lymphangiography, but symptoms related to this finding are rare. Although hairy cells are said to be slowly dividing and radioresistant, palliative radiotherapy has led to shrinkage of enlarged retroperitoneal, abdominal, and mediastinal lymphadenopathy, with relief of pain and lymphatic obstruction (5). However, patients with malignant peritoneal and pleural effusions may pursue a rapidly fatal course. Combination chemotherapy should be considered after splenectomy in patients with hairy cell leukemia with rapidly progressive disease. In light of this patient's favorable response, we feel that further investigation of ABVD is warranted.

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Roswell Park Memorial Institute Continuing Education Programs

Buffalo, New York, February–June, 1984

Roswell Park Memorial Institute is conducting monthly continuing education programs in oncology for community practitioners to disseminate information on the newest methods in the diagnosis and treatment of cancer. Each monthly seminar is organized by a different department of the Institute covering a different clinical specialty. These seminars qualify for Category I credit toward the AMA Physician's Recognition Award, prescribed credit by the American Academy of Family Physicians, and Category 2-D credit by the American Osteopathic Association. There is a $45.00 registration fee for 1-day seminars and a variable fee for longer programs. The seminars are cosponsored by the Cancer Control Program of the Institute and the American Cancer Society, New York State Division and Erie County Unit.

The seminars are scheduled as follows: Advances in Cancer Chemotherapy, *February 9, 1984* (Chairperson: Dr. Enrico Mihich); Tumors Involving the Skin, *April 12, 1984* (Chairperson: Dr. Ole Holtermann); Molecular Biology and Its Relevance to the Treatment of Colon Cancer, *May 12, 1984* (Chairperson: Dr. Arnold Mittelman); and Prevention of Cancer, *June 7, 1984* (Chairperson: Dr. Curtis Mettlin).

For further information, contact: Gayle Bersani, RN, Cancer Control Coordinator, Roswell Park Memorial Institute, 666 Elm St, Buffalo, NY 14263 (telephone: 716-845-4406).

Tenth Annual Fred J. Woods/St. Joseph's Community Cancer Center Lecture Series

Tampa, Florida, February 2–4, 1984

Comprehensive cancer treatment is this year's lecture series topic of discussion. Lectures will cover pathology, surgery, chemotherapy, and radiotherapy, and include panel discussions. Physicians of all disciplines are encouraged to attend.

The series is sponsored by the St. Joseph's Hospital of Tampa Foundation, Inc, University of South Florida, College of Medicine, and the American Cancer Society, Hillsborough County, Florida Unit. This continuing medical education offering meets criteria for 14 hours, Category 1 credits, as certified by the University of South Florida, College of Medicine. Registration is $75 and should be made payable to the St. Joseph's Hospital Foundation.

For further information, contact: Bruce Collison or Chuck Thomas, telephone 813-870-4340.

Intra-Arterial and Intracavitary Chemotherapy 1984

San Diego, California, February 24–25, 1984

This continuing medical education conference will take place at the Holiday Inn at the Embarcardero (San Diego, CA). The conference is approved for 14 hours of AMA/CMA credit as well as AAFP and the fee is $250.

For more information, contact: Office of Continuing Medical Education, UCSD School of Medicine, M-017, La Jolla, CA 92093.

Second International Conference on Adjuvant Chemotherapy in Breast Cancer

St. Gallen, Switzerland, March 1–3, 1984

There will be a maximum of 200 participants at this meeting representing all major study groups. The language is English.

For further information, contact: Sekretariat Prof. H. J. Senn, Medizinische Klinik C, Kantonsspital, CH-9007 St. Gallen, Switzerland (telephone: 071/26 10 62).

Infusional Cancer Chemotherapy: Techniques and Clinical Trials in Systemic and Regional Chemotherapy

Boston, Massachusetts, March 1–3, 1984

This course will take place at the New England Deaconess Hospital in Boston and is designed to develop the pharmacologic and cytokinetic rationale for continuous infusion delivery systems for cancer chemotherapy and to describe technologic advances involving arterial and venous access and the range of implanted and external portable pump delivery systems. A session will be devoted to clinical trials of systemic infusion chemotherapy employing short-term or protracted ambulatory delivery systems emphasizing comparative trials and impact on the therapeutic index. Newer applications of systemic infusion chemotherapy employing the simultaneous delivery of multiple drugs and infusion chemotherapy delivered in conjunction with concomitant radiation therapy will be discussed and the overall experience of infusion therapy in more than 300 patients reviewed.

Regional infusion chemotherapy will focus on recent experience with hepatic arterial infusion with a review of the collective experience at six centers in the United States through 1983. A detailed review of ongoing and future comparative trials will be presented. Special aspects of regional infusion for head and neck tumors as well as extremity and pelvic malignancies will be addressed. Expanded applications of the infusion schedule concept will be developed with presentations on microsphere delivery systems and intra-abdominal peritoneal chemotherapy ("belly bath"). Additional applications for delivery of analgesics and other medications will be discussed.

Finally, a workshop session emphasizing the practical aspects of developing an infusion chemotherapy program will include issues of comparative cost of chemotherapy delivery systems, the use of the infusion system for home chemotherapy, practical aspects of developing a nursing team to coordinate patient training, and a discussion of technical issues with regard to pharmacy support, venous and arterial access problem shooting, and pump management.

For further information, contact: Department of Continuing Education, Harvard Medical School, 25 Shattuck St, Boston, MA 02115 (telephone: 617-732-1525).

Sixty-Sixth Annual Meeting of the American Radium Society

San Diego, California, March 18–22, 1984

This meeting will take place at the Hotel Del Coronado in San Diego.

For more information, contact: Mrs. Sally R. Polek, Office of the Secretariat, American Radium Society, 925 Chestnut St, Philadelphia, PA 19107 (telephone: 215-574-3179).

Fourth International Conference on the Adjuvant Therapy of Cancer

Tucson, Arizona, March 21–24, 1984

This conference will be held at the Tucson Convention Center under the sponsorship of the University of Arizona Cancer Center. Drs. Stephen E. Jones and Sydney E. Salmon will serve as conference co-chairmen. The deadline for submission of abstracts, prepared in the AACR/ASCO format, is *November 1, 1983*.

For further information, contact: Mary Humphrey, Conference Coordinator, University of Arizona Cancer Center, Tucson, AZ 85724 (telephone: 602-626-6044).

Second International Conference on Malignant Lymphoma: Current Status and Prospects

Lugano, Switzerland, June 13–16, 1984

This conference, to be held at the Palazzo dei Congressi, will deal with all important approaches in the diagnosis and treatment of Hodgkin's and non-Hodgkin's lymphoma in children and adults. The lectures will be given primarily by invited speakers and selected controversial issues will be discussed by panels of leading experts. The program will include free presentations and a poster session.

Abstracts for free communications and the poster session, prepared according to the standard rules of AACR/ASCO, should be submitted to the address below no later than *January 15, 1984* for this conference. Abstracts will be selected for presentation by the conference organizing committee and advi-

sory board. Abstracts for the two workshops (cytogenetics and enzymology of neoplastic lymphoid cells) may also be submitted.

For further information, contact: F. Cavalli, MD, Division of Oncology, Ospedale San Giovanni, 6500 Bellinzona, Switzerland.

Fellowship in Medical Oncology, Hematology, or Combined Oncology-Hematology

July 1984 and July 1985

Applications are now being accepted for a fellowship program involving major teaching hospitals of Brown University's Program in Medicine, beginning July 1984 and July 1985. Clinical activities and opportunities for research are offered to qualified candidates with two years of approved medical residency and ABIM eligibility.

For further information, contact: F. J. Cummings, MD, Director, Division of Medical Oncology, or Manfred Steiner, MD, Director, Division of Hematology, Brown University, Box G, Providence, RI 02912.

Twentieth Congress of the International Society of Hematology

Buenos Aires, Argentina, September 1–7, 1984

The scientific program for the congress will be centered on fundamental issues of hematology and will consist of plenary sessions, symposia, workshops, and poster discussion sessions. Included in the congress week will be a two-day educational program.

Spanish and English will be the official languages.

For further information, contact: Twentieth Congress of the International Society of Hematology, Viamonte 2008, (1056) Buenos Aires, Argentina.

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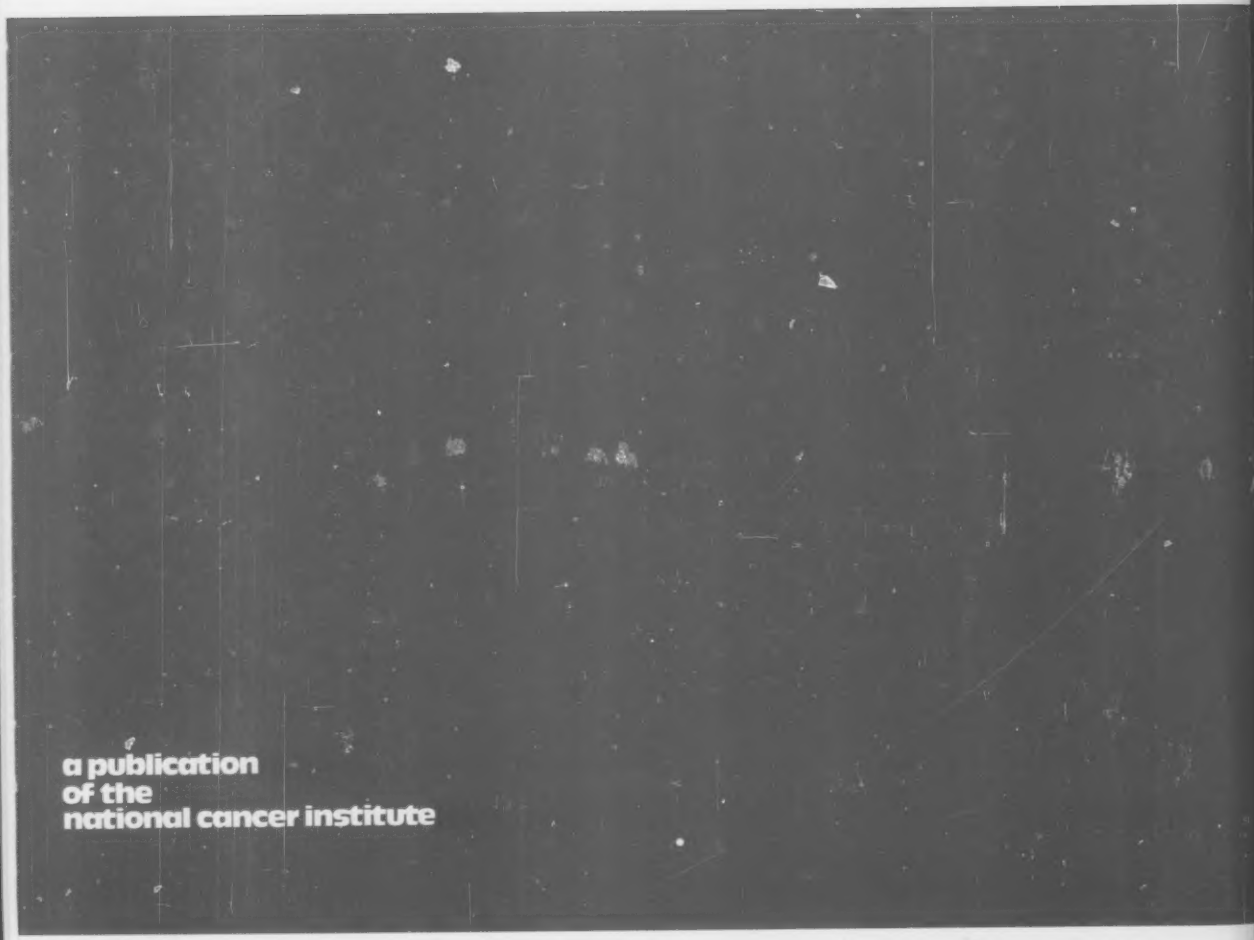

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